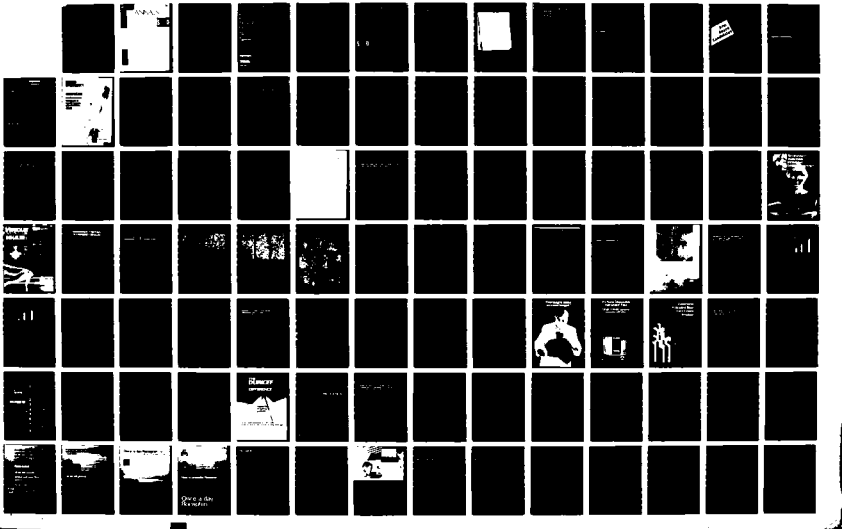
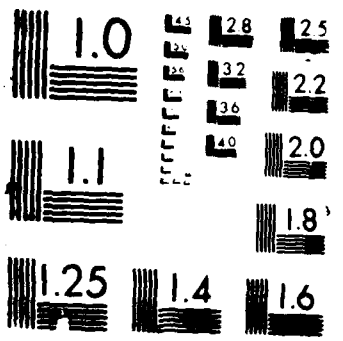
AD-A187 110 PROCEEDINGS OF THE UAEM/IRIEM RESEARCH SYMPOSIUM ON RESUSCITATION (1985)(U) UNIVERSITY ASSOCIATION FOR EMERGENCY MEDICINE LANSING MI AUG 85 DAMD17-85-G-5007 1/2

UNCLASSIFIED F/G 6/5 NL




1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0

ANNALS
OF EMERGENCY MEDICINE

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
CMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION PEPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION University Association of Emergency Medicine 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) University (Michigan State) 900 W. Ottawa Lansing, Michigan	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-85-G-5007
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62772A; PROJECT NO. 3S1-6277A874; TASK NO. AB; WORK UNIT ACCESSION NO. 281
11. TITLE (Include Security Classification) Scientific Symposium on Resuscitation 7-8 February 1985	
12. PERSONAL AUTHOR(S) Blaine C. White, M.C.	
13a. TYPE OF REPORT Proceedings	13b. TIME COVERED FROM 12/17/84 TO 9/30/85
14. DATE OF REPORT (Year, Month, Day) 1985 August	15. PAGE COUNT 185
16. SUPPLEMENTARY NOTATION	

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP
06	11	
06	05	

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
Injury; Casualty Management; Resuscitation; Trauma.

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This is to report on the 1985 combined Scientific Symposium on Resuscitation presented by the International Research Institute of Emergency Medicine (IRIEM) and the University Association for Emergency Medicine (UAEM) February 7-8, 1985, and supported in part by the Grant DAMD17-85-G-5007. Attached is the August 1985 issue of the Annals of Emergency Medicine which contains the complete 16 papers from the meeting.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION
22a. NAME OF RESPONSIBLE INDIVIDUAL Mrs. Virginia Miller	22b. TELEPHONE (Include Area Code) 301/663-7325 22c. OFFICE SYMBOL SGRD-RMI-S

DD Form 1473, JUN 86 *Previous editions are obsolete* SECURITY CLASSIFICATION OF THIS PAGE

- **Long duration of action**
- **Greater patient comfort[1]**
- **Reduced need for strong postoperative analgesics[2]**
- **Improved pulmonary functions[2]**
- **Reduced incidence of atelectasis[2]**
- **Use lowest dosage of local anesthetic to yield effective anesthesia**

Marcaine® HCl
(bupivacaine HCl injection, USP)
with or without epinephrine 1:200,000

Winthrop-Breon
WINTHROP-BREON LABORATORIES
90 Park Avenue, New York, N.Y. 10016

[1]0.25% only.

Please see adjacent important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

Marcaine® HCl
(bupivacaine HCl injection, USP) with or without epinephrine 1:200,000

PLEASE CONSULT FULL PRESCRIBING INFORMATION. A SUMMARY FOLLOWS:

CONTRAINDICATIONS: Obstetric paracervical block anesthesia, use in this technique has resulted in fetal bradycardia and death. Known hypersensitivity to the drug or to any amide-type local anesthetic, or to other components of MARCAINE solutions.

WARNINGS

THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF *ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.*

Local-anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection -intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended.

Mixing, or a prior or intercurrent use, of any other local anesthetic with *MARCAINE cannot be recommended* because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

PRECAUTIONS: General: *Safety and effectiveness* of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have I.V. fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

Epidural Anesthesia: The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. *During an epidural procedure, it is recommended that a test dose be administered* initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. Clinical conditions permitting, the test dose should contain epinephrine (10-15 μg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 mg of MARCAINE or an equivalent amount *of another local anesthetic to detect unintended intrathecal injection.* This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or, in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 μg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart block.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use *these agents concurrently, their combined action on the myocardium, the concentration and volume of* vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduction are potentially triggering agents for familial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene I.V. (see prescribing information before use), and other supportive measures.

Use in Head and Neck Area: Small doses of local anesthetics injected into the area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. *Confusion, convulsions, respiratory depression and/or* respiratory arrest, and cardiovascular stimulation or depression have been reported and may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored constantly, with resuscitative equipment and personnel immediately available if needed. Do not exceed dosage recommendations. (See DOSAGE AND ADMINISTRATION.)

Use in Ophthalmic Surgery: With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

Use in Dentistry: Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa; advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

Information for Patients: When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or other possible adverse occurrence noted in package insert.

Clinically Significant Drug Interactions *Administering* local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided; in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

(continued on next page)

87 11 3 085

Marcaine® HCl

(bupivacaine HCl injection, USP) with or without epinephrine 1:200,000

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)

Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.

Nursing Mothers: It is not known whether local anesthetics are excreted in human milk, because many drugs are, administer with caution.

Pediatric Use: Without further experience in children under 12, MARCAINE is not recommended for this group.

ADVERSE REACTIONS: A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

Systemic: The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System: Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.

Cardiovascular: High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)

Allergic: Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.

Neurologic: Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug used, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinals are characterized by leg paralysis, loss of consciousness, respiratory paralysis, and bradycardia. Effects following epidural or caudal anesthesia may include: spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, fecal and urinary incontinence, loss of perineal sensation and sexual function, persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery; headache, backache, septic meningitis, meningismus, slowing of labor, increased incidence of forceps delivery, cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

OVERDOSAGE: Acute emergency during therapeutic local anesthesia is generally related to high plasma levels or unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. *The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of **immediate** attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus I.V. injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg I.V. bolus of diazepam or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of I.V. fluids and, when appropriate, a vasopressor dictated by the clinical situation (eg, ephedrine or epinephrine to enhance myocardial contractile force).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis within a minute of onset. These observations suggest that O_2 consumption and CO_2 production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen. If not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur. Underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous in pregnant women. The parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished. (See Labor and Delivery in PRECAUTIONS.)

Composition of Marcaine Solutions: 0.25%—each mL contains 2.5 mg bupivacaine. 0.5%—each mL contains 5 mg bupivacaine. 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothioglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium.

References:

1. Buckley FP, Simpson BR. Acute traumatic and postoperative pain management. In Cousins MJ, Bridenbaugh PO (eds): *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia, JB Lippincott Co, 1980, chap 25.
2. Patel JM, Lanzafame RJ, Williams JS, et al. The effect of incisional infiltration of bupivacaine on pulmonary functions, atelectasis and narcotic need following elective cholecystectomy. *Surg Gynecol Obstet* 1983;157:338-340.

Winthrop-Breon

WINTHROP-BREON LABORATORIES
90 Park Avenue, New York, N.Y. 10016

Call for Abstracts
1986 Scientific Forum
American College of Emergency Physicians

Scientific papers in emergency medicine for presentation at the 14th Scientific Assembly of the American College of Emergency Physicians

September 15-18, 1986
Atlanta, Georgia

Deadline for submission of abstracts is May 9, 1986.

Mail five copies of the abstract to Scientific Papers Review Committee, American College of Emergency Physicians, PO Box 619911, Dallas, TX 75261-9911.

Abstracts may not exceed 250 words, and may not include figures or tables. The abstract should be typed double-spaced with 2-inch margins on 8½- x 11-inch bond paper. On a separate cover sheet, indicate abstract title; all authors and their affiliations; the name of the presenter; and the name, address, and telephone number of one author for purposes of negotiations regarding the abstract. Do not identify the author(s) in any way on the page containing the abstract. Any abstracts not meeting these criteria will be returned to the author immediately. Final manuscripts may be submitted, but must contain an abstract meeting these criteria.

A complete manuscript must be submitted no later than the day of presentation at the meeting. *Annals of Emergency Medicine*, the official journal of the American College of Emergency Physicians and the University Association for Emergency Medicine, reserves the right of first refusal on all scientific papers presented at the Scientific Assembly. If *Annals* does not notify authors, in writing, of the intent to publish by December 31, 1986, authors reserve the right to submit their papers to other publications. Information for authors on manuscript preparation and submission requirements may be found in each issue of *Annals*.

All presentations will be eligible for the $1,000 Micromedex Award for Best Original Scientific Paper, and all resident presentations will be eligible for the $250 *Annals* Best Resident Paper Award. The Scientific Papers Review Committee will select all award winners.

ANNALS
OF EMERGENCY MEDICINE

1985 UAEM/IRIEM PROCEEDINGS

SPECIAL CONTRIBUTIONS

CORRESPONDENCE

DEPARTMENTS

ANNALS OF EMERGENCY MEDICINE

AUGUST 1985
VOL 14, NO 8

Journal of the American College of Emergency Physicians and the University Association for Emergency Medicine

EDITORIAL OFFICE

Annals of Emergency Medicine
PO Box 619911
Dallas, Texas 75261-9911
214/659-0911

ABPA *Annals of Emergency Medicine* (ISSN 0196-0644) is published monthly for yearly subscription $50 USA and Canada, $25 resident and student, $60 foreign, $5 single copy, $25 ACEP and UAEM members (from membership dues) by the American College of Emergency Physicians, 1125 Executive Circle, Irving, Texas 75038-2522. Second class postage paid at Irving, Texas, and additional mailing offices. POSTMASTER: Send address changes to the American College of Emergency Physicians, PO Box 619911, Dallas, Texas 75261-9911.

Plan now to attend the 1985 Scientific Assembly

THE 1985 SCIENTIFIC ASSEMBLY LAS VEGAS, NEVADA, SEPTEMBER 9–12. **O**ver 125 outstanding courses presented by 105 nationally recognized faculty. **R**egistration fee for ACEP members reduced $45 from last year's fee. **R**egistration Fees: ACEP Member: $380; Physician Non-Member: $440; Nurses: $290; EMRA Members: $250; Others: $490. **B**asic and Advanced Financial Planning Seminar for spouses. **T**wenty-nine hours of ACEP Category I Credit available. **C**ore, intermediate and advanced courses available. **M**ore than 200 Technical and Scientific exhibits. **F**lexible scheduling. **Q**uest room rates at the MGM Grand Hotel $66 single or double. **D**iscounts on airfares through American Airlines. **F**or additional information on the meeting, contact the American College of Emergency Physicians, P.O. Box 619911, Dallas, Texas 75261-9911, (214) 659-0911.

So, You Want to Learn Toxicology?

Washington, DC
September 12-15

San Francisco
October 24-27

Denver
November 14-17

San Juan, Puerto Rico
December 12-15

We Teach It!

Comprehensive Review in Toxicology (CRIT)

A 4-day course for practitioners in Emergency Medicine, Family Practice, and Emergency Nursing, clinically oriented, and guaranteed to be fun,* covering all aspects of toxicology and poisonings. In addition to lectures, two days will be devoted to case presentations, with participants critiqued on their differential diagnoses and treatment regimens.

A cassette tape series for the didactic sessions listed below (days 1 & 2) is now available for your personal use. Produced by the Denver Institute of Clinical Toxicology, these tapes are professional quality, taped and edited in Denver. With each tape you order, you'll receive an outline of the program.

Instructor: Peter D Bryson, MD — Medical Director, Poison Treatment Center, and Emergency Medicine Staff, St Anthony Hospital Systems, Denver. Dr Bryson, who is board certified in toxicology, is a nationally-known speaker in the areas of toxicology and emergency medicine.

Sponsors: Denver Institute of Clinical Toxicology and St Anthony Hospital Systems.

Credit: Approved by ACEP, AMA, and AAFP for 20 hours Category I credit.

Tuition: Physicians $350**; Residents in training and nurses $325**

ORDER FORM

Sign me up for your _____ course _____ and make my reservation in the name listed below.
(city) (date)

My check money order (US funds) for _____ is enclosed.

_____ Please send me more information on courses.

Name: _____

Address: _____

_____

Phone: (_____) _____

CRIT, c/ Peter D Bryson, MD
22133 Crestmoor Road
Golden, CO 80401
303/526-1840

*Inquire about our "No-Fun" refund policy.
**A reduction in tuition is offered for early registration. Registration is limited; therefore, early registration is strongly recommended.

I would like to order _____ Single Tape(s) ($16)
_____ Three-tape Mini-Series ($42)
_____ Four-tape Midi-Series ($75)
_____ Twelve-Tape Series ($150)

on the sessions checked below:

___ 1. Management of the Overdosed Patient
___ 2. Pharmacokinetics Toxicokinetics
___ 3. Tricyclics/Anticholinergics
___ 4. Acetaminophen
___ 5. Salicylates
___ 6. Iron
___ 7. Cyanide Laetrile
___ 8. Alcohols Aniongap
___ 9. Insecticides
___ 10. Hydrocarbons
___ 11. Drugs of Abuse (2 tapes)

My check money order (US funds) for _____ is enclosed.

CALENDAR

For a list of ACEP Category I approved education programs available for HOME STUDY, contact Headquarters.

The following courses are automatically granted ACEP Category I credit on an hour-for-hour basis when following the American Heart Association protocol: ACLS Instructor; ACLS Provider; BCLS Instructor. The following courses are automatically granted ACEP Category I credit when following the American College of Surgeons protocol: ATLS Instructor (25 hr), ATLS Provider (19 hr).

Courses approved for ACEP Category I credit are indicated by ■. ACEP Category I approved credit hours are indicated in boldface after each listing. Color indicates ACEP-sponsored or -cosponsored courses.

The Calendar is prepared by the ACEP Education Department. For more information, contact Education Department, American College of Emergency Physicians, PO Box 619911, Dallas, TX 75261-9911; (214) 659-0911.

SEPTEMBER

■ **EMERGENCY CARE: AN EXTENDED WORKSHOP. September, 1985.** Boston, MA. Sponsor: Harvard Med Sch. Fee: $950. Contact: Barbara Wagner, MA Gen Hosp, Boston, MA 02114 (617) 726-3905. **(80)**

TOPICS IN EMERGENCY MEDICINE — 1985. September 4, 1985. Hanover, NH. Sponsor: Dartmouth-Hitchcock Med Ctr. Fee: $60-$75. Contact: Janet F. Thibodeau, Prog. Mgr, OCEHS, Dartmouth-Hitchcock Med Ctr, Hanover, NH 03756 (603) 646-5744.

■ **CHILDHOOD RESUSCITATION AND STABILIZATION. September 6-8, 1985.** Orlando, FL. Sponsor: ECE, Inc/Tampa Gen Hosp/USF Coll of Med/Tampa Em Assoc. Fee: $250. Contact: Natalia N. Cruz, MSN, ARNP, PO Box 18566, Tampa, FL 33679 (813) 251-6911. **(13)**

■ **CARDIOLOGY TUTORIALS IN THE WILDERNESS. September 7-14, 1985.** Colorado. Sponsor: UCSD Sch of Med. Fee: $395. Contact: Cindy Saxe, Off of CME, M-017, UCSD Sch of Med, La Jolla, CA 92093 (619) 452-3940. **(24)**

■ **SCIENTIFIC ASSEMBLY. September 9-12, 1985.** Las Vegas, NV. Sponsor: National ACEP. Fee: $380 ACEP Phys, Member; $440 Phys, Non-Member. Contact: Registrar, ACEP, PO Box 619911, Dallas, TX 75261-9911 (214) 659-0911. **(29)**

■ **CURRENT CONCEPTS IN EMERGENCY MEDICINE. September 13, 1985.** Richmond, VA. Sponsor: NC, ACEP & Coastal Found for Med Ed. Contact: Linda Bostic, 1250 N Lynn St, Ste 401, Arlington, VA 22209 (703) 841-0333. **(4)**

ATLS PROVIDER COURSE. September 13-14, 1985. Los Angeles, CA. Sponsor: ECEC. Fee: $475. Contact: ECEC, 4640 Admiralty Way #305, Marina del Rey, CA 90292 (213) 822-1312.

■ **COMPREHENSIVE REVIEW IN TOXICOLOGY. September 13-16, 1985.** Washington, DC. Sponsor: St Anthony's Hosp Sys, Denver Inst of Clinical Toxicology. Fee: $300-$350. Contact: Peter D Bryson, MD, Rt 5 Box 732 A, Golden, CO 80401 (303) 526-1840. **(20)**

■ **CARDIOLOGY TUTORIALS IN THE WILDERNESS. September 15-22, 1985.** Vermont. Sponsor: UCSD Sch of Med. Fee: $395. Contact: Cindy Saxe, Off of CME, M-017, UCSD Sch of Med, La Jolla, CA 92093 (619) 452-3940. **(24)**

■ **THE MANAGEMENT OF SEVERE TRAUMA. September 16-18, 1985.** Boston, MA. Sponsor: Harvard Med Sch, Dept of CE. Fee: To be determined. Contact: Norman Shostak, HMS Dept of CE, 641 Huntington Ave, Boston, MA 02115 (617) 732-1525. **(20)**

■ **BATTLEFIELD MEDICINE. September 16-20, 1985.** Brooks AFB, TX. Sponsor: Brooks AFB, TX. Contact: Patricia Sanner, MD, Maj, USAF, MC, USAFSAM/EDK, Brooks AFB, TX 78235-5000 (512) 492-6746. **(21)**

BOARD REVIEW COURSE. September 18, 1985. Phoenix, AZ. Sponsor: Emergency Physicians, Inc. Fee: TBA. Contact: Robert K. Nance, MD, 1744 E. Morten Avenue, Phoenix, AZ 85020 (602) 957-8047.

ENTREPRENEURIAL HEALTH CARE. September 19-20, 1985. San Francisco, CA. Sponsor: Law & Business Inc/Harcourt Brace Jovanovich, Pub. Fee: $395. Contact: Brenda D Kovatch, Sem Asst, Law & Business, 855 Valley Rd, Clifton, NJ 07013 (201) 472-7400.

■ **SEVENTH ANNUAL EMERGENCY PEDIATRICS. September 20-21, 1985.** Boston, MA. Sponsor: Boston Univ Sch of Med. Fee: $145-$220. Contact: Mary Hill, Dept of CME, Boston Univ Sch of Med, 80 E Concord St, Boston, MA 02118 (617) 247-5602. **(11.5)**

■ **VASCULAR AND PULMONARY DISEASES: DIAGNOSIS AND MANAGEMENT. September 20-22, 1985.** Las Vegas, NV. Sponsor: Univ of CO Sch of Med & Med Ed Resources. Fee: $190-$295. Contact: Stephen E. Mattingly, 5808 S Rapp St, Ste 202, Littleton, CO 80120 (303) 798-9682. **(13)**

■ **POSTGRADUATE INSTITUTE FOR EMERGENCY AND PRIMARY CARE PHYSICIANS-SYMPOSIUM I. September 23-27, 1985.** San Diego, CA. Sponsor: UCSD Sch of Med. Fee: $215-$440. Contact: Cindy Saxe, Off of CE, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940. **(33)**

■ **EMERGENCY MEDICINE REVIEW. September 23-28, 1985.** Omaha, NE. Sponsor: Univ of NE Med Ctr. Fee: $325-$475. Contact: Marge Adey, Ctr for CE, 42nd & Dewey Ave, Omaha, NE 68105 (402) 559-4152. **(45)**

■ **POSTGRADUATE INSTITUTE FOR EMERGENCY AND PRIMARY CARE PHYSICIANS-ADVANCED EMERGENCY MEDICINE PROCEDURES LABORATORY. September 24-26, 1985.** San Diego, CA. Sponsor: UCSD Sch of Med. Fee: $200. Contact: Cindy Saxe, Off of CE, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940. **(3)**

■ **FIRST NATIONAL CONFERENCE ON PEDIATRIC TRAUMA. September 26-27, 1985.** Boston, MA. Sponsor: Kiwanis Ped Trauma Inst, Kiwanis Intnl Found, New Eng Med Ctr. Fee: $385. Contact: Richard Murphy, PA, 171 Harrison Ave, Box 133, Boston, MA 02111 (617) 956-6380. **(16)**

- **ADVANCED CARDIAC LIFE SUPPORT PROVIDER COURSE. September 27-28, 1985.** Asheville, NC Sponsor Mountain Area Hlth Educ Ctr Fee $200 Contact Sherrill L Gentry, ACLS Admin Secy, Mountain Area Hlth Educ Ctr, 501 Biltmore Ave, Asheville, NC 28801 (704) 658-2677 **(16)**

- **SIMULATED ORAL BOARD SEMINAR. September 28, 1985.** Cincinnati, OH Sponsor OH ACEP Fee $200-$300 Contact Joan W Hess or Ex Dir 1395 E Dublin Rd Granville Rd #310 Columbus, OH 43229 (614) 846-0076 **(8)**

- **EMERGENCY MEDICINE UPDATE: WOUND REPAIR IN THE EMERGENCY DEPARTMENT. September 28, 1985.** Sponsor Univ of Pittsburgh Sch of Med, Div of CE & Ctr of Em Med of Western Pennsylvania Fee $75 Contact Molly T Vogt, PhD, Dir, Div of CE, 1022 Scaife Hall, Pittsburgh, PA 15261 (412) 624-2653 **(6.5)**

- **EMERGENCY MEDICINE REVIEW. September 28-October 2, 1985.** Columbus, OH Sponsor OH ACEP Fee $275-$475 Contact Joan W Hess or Ex Dir OH ACEP 1395 E Dublin Granville Rd Ste 310 Columbus, OH 43229 (614) 846-0076 **(49)**

- **SIMULATED ORAL BOARD SEMINAR. September 29, 1985.** Akron, OH Sponsor OH ACEP Fee $200-$300 Contact Joan W Hess or Ex Dir 1395 E Dublin Rd Granville Rd #310 Columbus, OH 43229 (614) 846-0076 **(8)**

- **THE CHILD AT RISK: PHYSICAL AND SEXUAL ABUSE. September 30-October 1, 1985.** Boston, MA Sponsor Boston Univ Sch of Med Fee $75 Contact Alicia Leahy, Dept of CME, Boston Univ Sch of Med 80 E Concord St, Boston, MA 02118 (617) 247-5602 **(12)**

OCTOBER

AEROSPACE MEDICINE PRIMARY COURSE. October 2-November 21, 1985. Brooks AFB, TX Sponsor USAF Sch of Aerospace Med Contact Christopher P Bell, USAFSAM/EDK, Brooks AFB, TX 78235 (512) 536-2844

- **EMERGENCY MEDICINE: CHALLENGING CLINICAL PROBLEMS.** October 3-6, 1985 Fallen Leaf Lake, CA Sponsor Univ of California Ofc of CME Fee TBA Contact Yvonne Majesko, Ofc of CME, School of Med 2701 Stockton Blvd, Sacramento, CA 95817 (916) 453-5390 **(16)**

- **SIMULATED ORAL BOARD SEMINAR.** October 5, 1985 [illegible] **(8)**

- **AN ADVANCED PEDIATRIC LIFE SUPPORT COURSE. October 7-9, 1985.** Baltimore, MD Sponsor Johns Hopkins Med Institutions Fee $375 Contact Noreen Javornik, Off of CE, Turner Bldg 720 Rutland Ave Baltimore MD 21205 (301) 955-6046 **(19)**

PREPARING FOR THE BOARDS — EMERGENCY MEDICINE 1985. October 7-11, 1985. [illegible]

- **EMERGENCY MEDICINE REVIEW. October 7-12, 1985.** Omaha, NE Sponsor Univ of NE Med Ctr Fee $325-$475 Contact Marge Adey, Ctr for CE 42nd & Dewey Ave, Omaha, NE 68105 (402) 559-4152 **(45)**

- **CURRENT TOPICS IN EMERGENCY MEDICINE. October 9-11, 1985.** Charlottesville, VA Sponsor EMS-Univ of VA Fee $200-$225 Contact Robert D Powers, MD, Box 523, UVA Hosp, Charlottesville, VA 22901 (804) 924-8485 **(15)**

THE SIXTH ANNUAL CONFERENCE ON CRITICAL CARE TRANSPORT. October 9-11, 1985. San Francisco, CA Sponsor Dept of Critical Care Transport, Stanford Univ Hosp & Contemporary Forums Fee $275-$295 Contact Margaret Blair, RN, BSN, Program Administrator, Contemporary Forums, 219 Canyon Vista Place, Danville, CA 94526 (415) 820-2800

CURRENT CONCEPTS IN EMERGENCY CARE. October 10-11, 1985. [illegible]

- **ATLS PROVIDER COURSE. October 10-11, 1985.** Kansas City, KS Sponsor Univ of KS Med Ctr Fee TBA Contact Jody Scott, Univ of KS Med Ctr, Dept of Surgery, 39th & Rainbow Blvd, Kansas City, KS 66103 (913) 588-6124 **(16)**

- **VASCULAR AND PULMONARY DISEASES: DIAGNOSIS AND MANAGEMENT. October 11-13, 1985.** Orlando, FL Sponsor Univ of CO Sch of Med & Med Ed Resources Fee $190-$295 Contact Stephen E Mattingly, 5808 S Rapp St, Ste 202, Littleton, CO 80120 (303) 798-9682 **(13)**

- **TEXAS CHAPTER WRITTEN BOARD PREPARATION COURSE. October 11 1985.** [illegible] (6)

- **ORAL BOARD EXAM PREP COURSE (INDIVIDUAL). October 12, 1985** [illegible] (8)

- **TEXAS CHAPTER ORAL BOARD COURSE. October 12, 1985.** [illegible] (8)

- **CARDIOPULMONARY EMERGENCIES. October 12-19, 1985.** Grand Cayman Island Sponsor UCSD Sch of Med Fee $275-$325 Contact Off of CME M-017 UCSD Sch of Med La Jolla, CA 92093 (619) 452-3940 **(21)**

BOARD REVIEW COURSE. October 16, 1985. Phoenix, AZ Sponsor Emergency Physicians Inc Fee TBA Contact Robert K Nimios, MD, 1741 E Morten Avenue, Phoenix, AZ 85020 (602) 952-8047

- **PEDIATRIC ADVANCED LIFE SUPPORT. October 24-25, 1985.** St Paul, MN Sponsor Childrens Hosp of St Paul, MN Fee $50-$150 Contact Leslie Fishman, MD 345 N Smith Ave St Paul, MN 55102 (612) 298-8236 **(16)**

CAMPBELL'S ENDURANCE SPORT AND FITNESS SYMPOSIUM. October 24-25, 1985. Kona, HI Sponsor Univ of California-Irvine Sch of Med Fee $95-$240 Contact J Massimino, MD, 896 Town and Country Office Park, Orange, CA 92668 (818) 999-3432

Philadelphia Examiners, Inc.

WRITTEN BOARD REVIEW

EMERGENCY MEDICINE

Attn: Board Candidates

The Philadelphia Examiners have prepared three hundred questions which we feel are of comparable difficulty to the ABEM exam. Two hundred questions are grouped by category and follow the percentages guideline given by ABEM (e.g., 13% cardiovascular, 7% trauma, etc.). Questions come complete with a separate booklet of novelette size answers and explanations of possible pitfalls.

Many physicians have expressed their special apprehension in the fields of toxicology and neurology. To meet this end we have included an additional fifty questions on toxicology focusing on the ingestions causing metabolic acidosis, hypersmolality, and delayed toxicity. A full twenty-five questions explore the differences of the stroke syndrome and the diagnostic clues of coma. Further questions round out your knowledge of meningitis in different age groups, vaginal bleeding in the different stages of pregnancy, and the distinctions of dementia, delirium, and behavioral disorders.

All of the answers are referenced in both Rosen's textbook, ***Emergency Medicine*** and the ACEP study guide. Studying one or both of these texts, followed by the review questions, will provide active feedback and help in the assessment of your core knowledge.

We have also prepared a unique set of professionally recorded audio cassettes. These six hours of written review invite active participation as the lectures are filled with questions for the listener. Pauses of sufficient time allow the examinee to answer. A comprehensive answer booklet is included. These cassettes should be listened to over and over again in the comfort of your home or automobile. Remember that repetition is st ill the mother of learning and nowhere is that more evident than in toxicology and pharmacology. A full ninety minutes is devoted to the intricacies of the alcohols, analgesics, mushrooms, plant toxins and street drugs. A well stocked memory bank with quick retrieval is essential to make that score of 75 closer.

☐ WRITTEN BOARD REVIEW $95.00
300 QUESTIONS WITH ANSWER BOOKLET.

☐ AUDIO CASSETTES $125.00
SIX HOURS OF LECTURES AND QUESTIONS WITH ANSWER BOOKLET

☐ BOTH $195.00

Philadelphia Examiners
P.O. Box 40124
Philadelphia, PA 19106
716/649-6423

Name _____

Address _____

City _____ State _____ Zip _____

VISA/Mastercard # _____ Exp. Date: _____

Signature _____

- **BASIC EKG INTERPRETATION. October 24-26, 1985.** Chattanooga, TN. Sponsor: Chattanooga Unit of Univ. of TN Coll. of Med. Fee: $250-$300. Contact: Margaret L. Clark, Chatta. Unit of UT Coll. of Med., 921 E. Third St., Ste. 400, Chattanooga, TN 37403 (615) 756-3370. **(17)**

- **THE FIRST NEW YORK CITY MARATHON SPORTS EMERGENCIES SYMPOSIUM. October 25-26, 1985.** New York, NY. Sponsor: NYU PG Med. Sch. Fee: $143-$190. Contact: Sandra Peterfreund, NYUPGMS, 550 First Ave., New York, NY 10016 (212) 340-5295. **(11)**

  THE 1ST ANNUAL REGIONAL VASCULAR CONFERENCE: ADVANCES IN VASCULAR SURGERY. October 25-26, 1985. Knoxville, TN. Sponsor: Knoxville Unit, The Univ. of Tennessee Coll. of Med., Dept. of CME. Fee: $175-$250. Contact: James Newby or Kay Chase, D-116, 1924 Alcoa Highway, Knoxville, TN 37920 (615) 544-9190.

- **VASCULAR AND PULMONARY DISEASES: DIAGNOSIS AND MANAGEMENT. October 25-27, 1985.** Hilton Head, SC. Sponsor: Univ. of CO Sch. of Med. & Med. Ed. Resources. Fee: $190-$295. Contact: Stephen E. Mattingly, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120 (303) 798-9682. **(13)**

- **ACLS PROVIDER COURSE. October 28-29, 1985.** Long Beach, CA. Sponsor: Emergency Care Ed. Ctr., Inc. Fee: $100-$225. Contact: ECEC, 4640 Admiralty Way #305, Marina del Rey, CA 90292 (213) 822-1312. **(16)**

- **POSTGRADUATE INSTITUTE FOR EMERGENCY AND PRIMARY CARE PHYSICIANS-SYMPOSIUM III. October 28-November 1, 1985.** San Diego, CA. Sponsor: UCSD Sch. of Med. Fee: $215-$440. Contact: Cindy Saxe, Off. of CE, M-017, UCSD Sch. of Med., La Jolla, CA 92093 (619) 452-3940. **(33)**

- **POSTGRADUATE INSTITUTE FOR EMERGENCY AND PRIMARY CARE PHYSICIANS-ADVANCED EMERGENCY MEDICINE PROCEDURES LABORATORY. October 29-31, 1985.** San Diego, CA. Sponsor: UCSD Sch. of Med. Fee: $200. Contact: Cindy Saxe, Off. of CE, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940. **(3)**

- **EMS TODAY. October 30-November 1, 1985.** Atlanta, GA. Sponsor: UCSD Sch. of Med. Fee: $210-$240. Contact: Catherine Petocchi, Off. of CME, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940. **(15)**

- **EMERGENCY ASSESSMENT, DIAGNOSIS AND CARE. October 30-November 18, 1985.** [illegible] **(30)**

NOVEMBER

ATLS PROVIDER COURSE. November 1-2, 1985. Los Angeles, CA. Sponsor: ECEC. Fee: $475. Contact: ECEC, 4640 Admiralty Way #305, Marina del Rey, CA 90292 (213) 822-1312.

- **FIFTH ANNUAL SOUTHWESTERN POISON SYMPOSIUM. November 1-3, 1985.** Tucson, AZ. Sponsor: AZ Poison Control Syst., Univ. of AZ Coll. of Pharm., St. Luke's Hosp. Fee: $50-$135. Contact: Off. of CME, Univ. of AZ Coll. of Med., Tucson, AZ 85724 (602) 626-6173. **(19)**

- **26TH WORKSHOP IN ELECTROCARDIOGRAPHY. November 1-4, 1985.** Clearwater Beach, FL. Sponsor: Rogers Heart Found. Fee: $225. Contact: Anne Criss Taylor, 601 12th St. No., St. Petersburg, FL 33705 (813) 894-0790. **(19)**

- **ACLS PROVIDER COURSE. November 2-3, 1985.** Tampa, FL. Sponsor: Em Care Ed. Inc. of FL, USF Coll. of Med. Fee: $185. Contact: Natalia N. Cruz, RN or Susan Gould, RN, PO Box 18566, Tampa, FL 33679 (813) 251-6911. **(16)**

  PEDIATRIC EMERGENCY MEDICINE. November 4-8, 1985. Philadelphia, PA. Sponsor: Univ. of PA Sch. of Med. Fee: $450-$700. Contact: PS Pasquariello, Jr., MD, Children's Hosp. of Phila., Philadelphia, PA 19104 (215) 596-9178.

  15TH ANNUAL CLINICAL CONFERENCE: TOPICS IN EMERGENCY MEDICINE. November 7-8, 1985. [illegible]

- **ACLS PROVIDER RECERTIFICATION COURSE. November 8, 1985.** [illegible] **(8)**

- **ACLS INSTRUCTOR COURSE. November 9, 1985.** [illegible] **(8)**

- **COMPREHENSIVE REVIEW IN TOXICOLOGY. November 14-17, 1985.** Denver, CO. Sponsor: St. Anthony's Hospital Systems, Denver Institute of Clinical Toxicology. Fee: $300-$350. Contact: Peter D. Bryson, Rt. 5 Box 732-A, Golden, CO 80401 (303) 526-9200. **(20)**

- **ATLS REFRESHER COURSE. November 15, 1985.** Kansas City, KS. Sponsor: Univ. of KS Med. Ctr. Fee: TBA. Contact: Jody Scott, Univ. of KS Med. Ctr., Dept. of Surgery, 39th & Rainbow Blvd., Kansas City, KS 66103 (913) 588-6124. **(8)**

- **COMPREHENSIVE REVIEW IN EMERGENCY MEDICINE: SURGERY-TRAUMA. November 15-19, 1985.** [illegible] **(40)**

- **MANAGEMENT STRATEGIES IN EMERGENCY MEDICINE. November 18-20, 1985.** [illegible] **(25)**

  BOARD REVIEW COURSE. November 20, 1985. Phoenix, AZ. Sponsor: Emergency Physicians Inc. Fee: TBA. Contact: Robert K. Nance, M.D., 1241 E. Morten Avenue, Phoenix, AZ 85020 (602) 995-8047.

- **VASCULAR AND PULMONARY DISEASES: DIAGNOSIS AND MANAGEMENT. November 22-24, 1985.** Key Biscayne, FL. Sponsor: Univ. of CO Sch. of Med. & Med. Ed. Resources. Fee: $190-$295. Contact: Stephen E. Mattingly, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120 (303) 798-9682. **(13)**

DECEMBER

- **CURRENT CONCEPTS IN EMERGENCY CARE. December 1-6, 1985.** Maui, HI. Sponsor: WA ACEP/Inst for Em Med Ed. Fee: $200-$350. Contact: Georgine Fleck, *Kailani World Travel, 4192 Meridian, Bellingham, WA 98227 (800) 426-2561 US (800) 562-2597 WA.* **(25)**
- **ACLS COURSE '85. December 2-4, 1985.** Robbinsdale, MN. Sponsor: N Mem Med Ctr. Fee: $100-$150. Contact: Sally Sattler, 3300 Oakdale Ave, Robbinsdale, MN 55422 (612) 520-5451 **(16)**
- **NEONATAL RESUSCITATION PROGRAM. December 5, 1985.** Robbinsdale, MN. Sponsor: N Mem Med Ctr. Fee: $60-$120. Contact: Peter Marshall, MD, N Mem Med Ctr, 3300 Oakdale Ave, Robbinsdale, MN 55442 (612) 520-5451 **(8)**
- **VASCULAR AND PULMONARY DISEASES: DIAGNOSIS AND MANAGEMENT. December 6-8, 1985.** Las Vegas, NV. Sponsor: Univ of CO Sch of Med & Med Ed Resources. Fee: $190-$295. Contact: Stephen E Mattingly, 5808 S Rapp St, Ste 202, Littleton, CO 80120 (303) 798-9682 **(13)**
- **VASCULAR AND PULMONARY DISEASES: DIAGNOSIS AND MANAGEMENT. December 6-8, 1985.** San Diego, CA. Sponsor: Univ of CO Sch of Med & Med Ed Resources. Fee: $190-$295. Contact: Stephen E Mattingly, 5808 S Rapp St, Ste 202, Littleton, CO 80120 (303) 798-9682 **(13)**
- **POSTGRADUATE INSTITUTE FOR EMERGENCY AND PRIMARY CARE PHYSICIANS-SYMPOSIUM II. December 9-13, 1985.** San Diego, CA. Sponsor: UCSD Sch of Med. Fee: $215-$440. Contact: Cindy Saxe, Off of CE, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940 **(33)**
- **POSTGRADUATE INSTITUTE FOR EMERGENCY AND PRIMARY CARE PHYSICIANS-ADVANCED EMERGENCY MEDICINE PROCEDURES LABORATORY. December 10-12, 1985.** San Diego, CA. Sponsor: UCSD Sch of Med. Fee: $200. Contact: Cindy Saxe, Off of CE, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940 **(3)**

  ADVANCED TRAUMA LIFE SUPPORT (PROVIDER). December 13-14, 1985. Los Angeles, CA. Sponsor: ECEC. Fee: $475. Contact: ECEC, 4640 Admiralty Way #305, Marina del Rey, CA 90292 (213) 822-1312
- **TRAUMA UPDATE '85. December 13-14, 1985.** Albuquerque, NM. Sponsor: Univ of NM Sch of Med Burn & Trauma Unit, NM Com on Trauma. Fee: $150. Contact: Gerald B Demarest, MD, UNM Hosp, Dept of Surg, 2211 Lomas, NE, Albuquerque, NM 87131 (505) 843-2270 **(9)**

  BOARD REVIEW COURSE. December 18, 1985. Phoenix, AZ. Sponsor: Emergency Physicians Inc. Fee: TBA. Contact: Robert K Nimlos, MD, 1741 E Morten Avenue, Phoenix, AZ 85020 (602) 952-8047

JANUARY 1986

- **POSTGRADUATE INSTITUTE FOR EMERGENCY & PRIMARY CARE PHYSICIANS-SYMPOSIUM I. January 13-17, 1986.** San Diego, CA. Sponsor: UCSD Sch of Med. Fee: $215-$440. Contact: Cindy Saxe, Off of CME, M-017, UCSD Sch of Med, La Jolla, CA 92099 (619) 452-3940 **(33)**
- **TEXAS CHAPTER ORAL BOARD COURSE. January 18, 1986.** Dallas, TX. Sponsor: TX ACEP. Fee: $215-$275. Contact: Ruth Hargrove Dean, TX ACEP, PO Box 610717, Dallas, TX 75261-0717 (214) 255-2156 **(8)**
- **CARDIOLOGY TUTORIALS IN THE WILDERNESS. January 18-25, 1986.** Florida. Sponsor: UCSD Sch of Med. Fee: $395. Contact: Cindy Saxe, Off of CME, M-017, UCSD, La Jolla, CA 92093 (619) 452-3940 **(24)**
- **PROBLEMS IN INFECTIOUS DISEASE & TOXICOLOGY. January 18-25, 1986.** Kona, HI. Sponsor: UCSD Sch of Med. Fee: $250-$265. Contact: Edith S Bookstein, PO Box 2586, La Jolla, CA 92038 (619) 454-3212 **(21)**
- **9TH ANNUAL NEUROLOGY FOR NON-NEUROLOGISTS. January 29-31, 1986.** San Diego, CA. Sponsor: UCSD Sch of Med. Fee: $350-$400. Contact: WC Wiederholt, MD, UCSD M024, La Jolla, CA 92093 (619) 452-6224 **(21)**

Foreword

In writing a preface to the publication of the manuscripts from the 1985 UAEM/IRIEM Research Symposium, which it was my pleasure to chair, I have decided to share a reflection on the nature and role of science in emergency medicine.

In science, we attempt to grasp at the nature of reality with observations. What we may easily miss is that, while our observations are existentially certain (we saw what we saw), our grasp on the nature of the reality reflected in the observation (the hypothesis) is forever radically uncertain. The fact that something has happened is clear; exactly what it is that happened is not.

Thus in science one is continuously engaged in the dialectic described by Hegel:

1. It is like so (A);
2. It is not like so (not A);
3. Ah - so (like B).

And Ah - so becomes the first impression of a new series. Scientists are engaged in a conversation with and about reality in which the current understanding is always surpassed.

Understanding this is critical to growth; we must become personally comfortable with radical uncertainty about the nature of reality. In other words, we'll all get it wrong. A good hypothesis accounts for several diverse observations, and is amenable to further testing. We can never prove the hypothesis; rather, we design tests of the hypothesis (ideas about the nature of reality) which give us the opportunity to make new observations that might falsify the hypothesis. Good scientific design, then, is aimed at the possibility of being able to say, "It is not like so."

History is helpful in understanding this. The dark ages come when we assert that our grasp on reality is certain and right, and when we enforce that assertion by structural or legal means. Enlightenment occurs when we admit our radical uncertainty. Advancement comes when we can freely say, "It is not like so. Ah - so," as did Copernicus, Galileo, Newton, Kepler, Pasteur, Lister, Michelson and Morley, Einstein, Freud, Schredinger, Watson and Crick, Kung, and many others.

What you will read in the following pages is not likely to provide ready, practical formulas (protocols) to solve our problems, nor is this conversation with and about reality concerned with any petty socioeconomic-political agenda. Rather, here is a discussion about the reality we engage when we try to resuscitate patients. Here is the driving conceptual process by which the future of emergency medicine will be formed and ensured.

Specifically in these terms, I especially want to thank the participants for their commitment to the study of resuscitation issues. I have learned from and admired each of them. The leaders of UAEM and IRIEM deserve our thanks for their support. The US Army Medical Research and Development Command, in the person of Colonel Tom Camp, MD, supported this symposium with a grant which made it all possible, and we are grateful.

I also want to thank *Annals of Emergency Medicine* for providing prompt publication. Editor Ronald Krome, MD, and Managing Editor Nancy Perkin have been tremendous and gracious in their assistance.

We invite you to read, enjoy, and ponder this conversation with, and about, the nature of the reality underlying the work and future of emergency medicine in resuscitation.

Blaine C White, MD
Special Issue Editor
Associate Professor, Emergency Medicine
Michigan State University College of Human Medicine
East Lansing, Michigan

Session 1: Shock

It is fascinating that shock, considered at one time to have been "researched out," is now fully resuscitated as a field of study. It would seem that not all the questions have been answered; more importantly, neither have all the questions been raised.

I would guess that the new (or rather, the continuing) interest in cerebral and cardiac resuscitation has generated new interest in this older topic. Early investigations examined a wide variety of possible therapeutic avenues, without a complete understanding of the pathophysiology of the problem. As bits and pieces of the shock puzzle fell into place, some therapies were replaced by others that were considered newer or more contemporary. But all the data are never in, and investigations into the field are now entering into a new phase at the cellular level.

The UAEM/IRIEM panel that dealt with shock represented a variety of investigators examining shock at both the clinical level and the cellular level. Their papers, which are here available for scrutiny, will likely open new vistas of research. Clinicians and investigators should profit from their work while maintaining a historical perspective on the problem.

A cursory review of the past 20 years of shock research suggests that we have gone from every shock patient getting vasopressors to every shock patient getting crystalloids or colloids, depending on which school you believe in. Now we are tailoring therapy to the patient's problem, as best identified in the clinical picture. We have gone from no hemodynamic monitoring to monitoring all hemodynamic parameters, with catheters inserted into both natural and unnatural openings. Blood gas studies, which were virtually nonexistent ten to 20 years ago, are now a standard of care in virtually all emergency departments and intensive care units.

Dr Robert Wilson, who has done work in this area for a long time, has very nicely reviewed the clinical problems related to shock, and has summarized the current clinical status of monitoring and therapy. He has stressed for us the high mortality associated with this syndrome, a mortality that has improved only slightly. Most improvement has been in the area of hypovolemic and hemorrhagic shock related to trauma. There can be little doubt that the best treatment is prevention, with the limitation of blood loss by early surgical intervention. Rapid fluid repletion while controlling continued blood loss still would appear to be the best therapy.

Although naloxone may hold some future promise, its value in hypovolemia during shock but prior to arrest has not been fully elucidated. Naloxone (and perhaps other opioids) may play a role in the improvement of the patient's hemodynamic state in a variety of shock states. Dr Bernton's paper examines these findings, and provides a nice review and stimulus for future study. We are perhaps just beginning to break ground in this arena.

Perhaps the area of study that offers the most challenge and opportunity for new therapeutic avenues is elemental-cellular study. The role of calcium, which has received a great deal of attention recently, was discussed by the panel and is presented here. It seems, as Dr Wilson points out, that shock is a cellular disease, and thus it requires cellular therapy (ie, therapy should be directed to improving the function of the cells). Although blood flow and oxygenation are important elements of cellular function, the ability of the cells to perform cellular energy function also may depend on a variety of so-called "trace" elements. Among those now being studied are calcium, magnesium, and iron.

Unlike Mr Spock of "Star Trek" fame, whose metabolism was based on copper (in addition to having his heart on the wrong side), ours would appear to be not only carbon-based, but iron-based. Who knows what changes in iron cellular metabolism occur as a result of impaired oxygenation at the cellular level? Can it be reversed?

The pulmonary effects of shock and its sequelae are outlined in Dr Ward's paper on adult respiratory distress syndrome. The pleomorphic effects of shock do not appear to be targeted at a specific organ, but rather they seem to involve a variety of organ systems. These include not only the lungs, but also the kidneys, heart, and brain. This is a fact that should surprise no one, for recent and past studies have all supported the cellular nature of this entity.

The past ten years in shock research have taken us from knowledge that all the significant questions were answered to wonder at the cellular basis of all life, including the homeostasis of the organism. The new frontiers of research seem to include cellular energy and cellular life, with the so-called "trace" elements perhaps playing a dominant role in injury and resuscitation of the entire organism.

Ronald L Krome, MD
Chief, Department of Emergency Medicine
William Beaumont Hospital
Royal Oak, Michigan

SPECIAL CONTRIBUTION
intravascular volume; shock;
tissue perfusion

Science and Shock: A Clinical Perspective

[Wilson RF: Science and shock: A clinical perspective. Ann Emerg Med August 1985;14:714-723.]

Robert F. Wilson, MD
Detroit, Michigan

From the Department of Surgery, Detroit Receiving Hospital and Wayne State University School of Medicine, Detroit, Michigan

Presented at the 1985 UAEM/RIEM Research Symposium in Orlando, Florida, February 7-8, 1985

Address for reprints: Robert F. Wilson, MD, Department of Surgery, Wayne State University, 4201 St Antoine, Detroit, Michigan 48201

INTRODUCTION

Shock that is not readily reversed with fluid administration may be associated with mortality rates as high as 70% to 90%. Early diagnosis and rapid, aggressive therapy offer the best chance for success in these critically ill patients. Physicians working in emergency departments are at a particular disadvantage in that they must often make a diagnosis and begin therapy with little or no baseline data or clinical information.

Shock generally is associated with inadequate tissue perfusion; however, many patients with shock who are in early sepsis[1,2] and some who have acute myocardial infarction[3,4] do not have the cold clammy skin and excessive vasoconstriction characteristic of low cardiac output and poor perfusion.

Cardiac output measured in patients in early septic shock is often found to be normal or increased, and the total peripheral vascular resistance is usually quite low.[1] The skin, as might be expected in such a hemodynamic situation, tends to be warm and dry, and this type of shock has been referred to as warm or hyperdynamic septic shock. On the other hand, some of these septic patients will go on to develop a low cardiac output, excessive vasoconstriction, and cold, clammy skin. When hypovolemia is corrected in this hypodynamic group, the cardiac output may rise relatively rapidly to normal or hyperdynamic levels.

Thus shock might best be defined as a severe pathophysiologic abnormality with abnormal cellular metabolism which is usually due to poor tissue perfusion, but may also be caused by such other factors as sepsis. The conceptualization of shock in biochemical terms has the advantage of de-emphasizing the cardiovascular changes. These may not be clinically apparent until relatively late. Stressing biochemical changes that tend to occur much earlier forces closer scrutiny of the patient.

DIAGNOSIS

The criteria most frequently used to diagnose shock clinically are the following: 1) a systolic blood pressure of less than 80 or 90 mm Hg, 2) severe oliguria, 3) metabolic acidosis, and 4) evidence of poor tissue perfusion (cold, clammy skin or clouded sensorium). Unfortunately these signs are often not detectable until relatively late, particularly if the patient is septic. If the diagnosis of shock is delayed until all or most of these signs are present, the chances for a successful outcome are greatly reduced, particularly in septic patients.

Blood Pressure

Systolic, Pulse & Diastolic Pressures

The arterial blood pressure is evaluated in three parts: diastolic pressure, which correlates with the amount of arteriolar vasoconstriction present; pulse pressure (the difference between the systolic and the diastolic pressures), which is primarily related to stroke volume and to the rigidity of the aorta and its larger branches; and systolic pressure, which is determined by a combination of all these factors. Of the three, pulse pressure is the most important because it provides some indication as to whether blood flow is

increasing or decreasing. Although cardiac output and stroke volume tend to decrease with advancing age, pulse pressure tends to rise in the elderly because of increasing rigidity of the aorta and its larger branches. Stroke volume and pulse pressure correlate poorly when large groups of patients are analyzed; in an individual patient, however, changes in pulse pressure often correlate well with changes in stroke volume. For example, if a patient's blood pressure changes from 120/80 to 120/100 mm Hg, the stroke volume may have decreased by as much as 50%.

Pressure Changes with Hemorrhage

In hypovolemic shock, major decreases in stroke volume (and hence pulse pressure) often occur long before there is any significant fall in the systolic pressure. Diastolic pressure generally rises initially with hemorrhage. This is caused by increased sympathoadrenal stimulation.[5] Consequently, even though stroke volume and pulse pressure decrease, systolic pressure may be relatively well maintained. Because the potential for vasoconstriction is limited, continued blood loss will eventually result in a significant decrease in both systolic and diastolic pressures.

In previously normal patients, systolic pressure is often maintained relatively well until a blood volume deficit of at least 15% to 25% has developed.[6] Thus, in the average 70-kg man with a normal blood volume of 5,000 mL, a rapid blood loss of 500 to 1,000 mL may cause some decrease in pulse pressure. Systolic pressure often does not fall significantly until more than 1,500 to 2,000 mL of blood have been lost and the blood volume deficit exceeds 25%. Thus, if a patient who is hypotensive from hypovolemia is given just enough fluid to restore his systolic blood pressure to relatively normal values, he probably still has a blood volume deficit of at least 1,000 mL. If the hypotension has been present for more than 30 minutes, the patient probably also has a much greater interstitial fluid deficit. If this fluid is not adequately replaced, tissue perfusion will be reduced, and severe hypotension may reappear rapidly if there is even mild additional fluid or blood loss.

In the great majority of patients with an unobtainable cuff blood pressure, systolic blood pressure is extremely low, often less than 50 mm Hg; in the remaining 5% to 10%, intraarterial pressure may be relatively normal or even high.

Intraarterial Blood Pressure

If any difficulty is encountered in obtaining a consistent and clear cuff blood pressure, and if the patient's condition does not improve rapidly with therapy, an intraarterial catheter should be inserted.

Although the mean pressure obtained with a radial artery catheter usually correlates rather well with the central aortic pressure, the pulse pressure and systolic blood pressure obtained with a radial artery line is often more than 10 to 20 mm Hg higher than central aortic blood pressure. Thus cuff blood pressure often correlates better with central arterial blood pressure than does a radial artery blood pressure. Consequently there is increasing use of catheter insertion into more proximal arteries, such as the axillary artery (using the Seldinger technique), or the aorta itself to obtain more accurate measurements.

Urine Output

Correlation with Cardiac Output

The timed urine output (without diuretics) often correlates well with the renal blood flow, which in turn is dependent on cardiac output. With any decrease in renal blood flow or pressure, the renal arterioles constrict, thereby reducing glomerular blood flow. In addition, renal blood flow during hypovolemia tends to shift from the outer renal cortex to the juxtamedullary portions of the kidney,[7] where the glomeruli are fewer in number and have longer loops of Henle. This shift in renal blood flow results in an increased absorption of sodium and water.

Urine Sodium and Osmolarity

In patients who become hypovolemic and have a reduced renal perfusion, the urine sodium concentration may fall and the urine osmolarity rise significantly before there is a decrease in urine output.[8] If the urine sodium falls rapidly or is less than 10 to 20 mEq/L, the kidneys are usually functioning relatively well but are not being satisfactorily perfused.

Acid-Base Changes

Respiratory Alkalosis

The classic acid-base abnormality in established shock is metabolic acidosis. It is now recognized, however, that early shock is characterized by respiratory alkalosis, particularly if sepsis is present. The respiratory alkalosis is generally not a compensatory mechanism for acidosis or hypoxia; it is a nonspecific response. If the PCO_2 is driven below 25 mm Hg, this severe hypocapnia may in itself cause hemodynamic impairment, especially reduction of cerebral blood flow.

Metabolic Acidosis

As shock progresses, anerobic metabolism results in lactate accumulation and development of metabolic acidosis. Blood lactate determinations may be very helpful as an indicator of the patient's progress and prognosis.[9]

In the early phases of the metabolic acidosis, the acid-base abnormality can often be corrected simply by improving tissue perfusion. Later, however, correction by administration of sodium bicarbonate may be necessary, particularly if the arterial pH falls below 7.10.

Combined Metabolic & Respiratory Acidosis

In the final stages of shock, blood gas analyses typically show an elevated PCO_2, a low HCO_3^-, and a very low pH. If a combined metabolic and respiratory acidosis is allowed to develop, the prognosis for ultimate survival is extremely poor,[10] even if the pH can be restored to normal with various drugs, such as Tris buffer.[11]

Tissue Perfusion

Stroke Volume & Pulse Pressure

As mentioned previously, one can follow changes in stroke volume by observing the changes in pulse pressure and by noting the ease with which the peripheral pulses can be palpated. In an individual patient, changes in pulse pressure often reflect changes in the stroke volume relatively well, and are thus a much better indication of blood flow than is systolic pressure, particularly in early shock.

Skin Changes

Cold and clammy skin all over the body generally indicates that the patient has a low cardiac output and a high total peripheral vascular resistance secondary to intense sympathoadrenal stimulation.

Mentation

A clouded sensorium and increasing lethargy can usually be considered as signs of poor tissue perfusion, and not infrequently these are the first indication that a patient is becoming septic. In contrast, an alert, interested individual can be assumed to have good cerebral perfusion. Our experience is that such an individual is much more likely to survive, even though his laboratory values may be quite abnormal.

AV Oxygen Differences

If the AV oxygen difference is less than 3.0 vol%, cardiac output is usually greater than normal (probably above 4.5 L/min/m^2). Even without calculating the AV differences in oxygen content, one can determine if the cardiac output is rising or falling by watching the changes in the mixed venous oxygen saturation or PO_2.[12]

Although pulmonary arterial blood is preferable to CVP blood for estimating cardiac output from AV oxygen differences, we have found little difference between the two unless the cardiac output is very high or very low.

TREATMENT

Correction of Primary Process

Although one may have to begin treatment of shock without knowing its initial cause, a strong effort should always be made to establish an accurate etiologic diagnosis as soon as possible. Bleeding and sepsis must be controlled rapidly if resuscitation is to be successful.

If the administration of 3,000 mL of a balanced electrolyte in 15 minutes to a trauma victim does not restore the BP to at least 100 mm Hg, the patient is usually bleeding rapidly somewhere. If the source is not apparent (eg, multiple fractures), the likely source is the abdomen and urgent surgery should be considered.

Septic foci such as abscesses must be eliminated as rapidly as possible. Surgery is much more important than antibiotics. The most frequent cause of death from sepsis is failure to drain a septic focus before severe vital organ damage has occurred.[13] In some instances these patients may seem too sick to tolerate any surgery, however, we believe that such patients are usually "too sick not to have surgery." After an expeditious, aggressive effort to optimize their condition, such patients should be taken to surgery on an emergency basis.

The importance of the patient's preshock condition must also be emphasized. McCabe and Jackson[14] classified underlying diseases associated with sepsis as rapidly fatal, ultimately fatal, and nonfatal. Fried and Vosti[15] applied this classification to 270 patients with gram-negative bacteremia, of whom 34% had shock. For diseases that were "rapidly fatal," such as acute leukemia, postnecrotic cirrhosis, and bacterial endocarditis, the mortality was 86%. In the "ultimately fatal" group, with diseases such as lymphoma and various other malignancies, the mortality was 46%. In the "nonfatal" category, which included patients with nonmalignant disease of the urinary and gastrointestinal tracts and septic abortion, the mortality rate was only 16%.

Resuscitation Efforts

Ventilation

In any critically ill or injured patient, the first priority of resuscitation is to ensure a patent airway and adequate ventilation. Adequate ventilation in the patient who has shock or sepsis is usually at least one-and-one-half to two times normal.[16,17]

In our studies of patients admitted with thoracic trauma, shock by itself on admission was associated with an eventual mortality of about 7%. If shock was present with acute respiratory distress requiring ventilatory assistance, the mortality rate was 69%.[18]

The importance of ventilatory assistance in shock, particularly if increased respiratory effort is required, was shown by Aubier et al[19] in experimental cardiogenic shock in dogs. Spontaneously ventilating animals developed higher lactic acid levels and had lower survival rates than did similar dogs given ventilatory assistance.

Some of the more frequent indications for ventilatory assistance for patients in shock include:[20]

1) minute ventilation less than 6 to 8 L/min, 2) tidal volume less than 4 mL/kg, 3) vital capacity less than 10 mL/kg, 4) PaCO$_2$ greater than 45 mm Hg if a metabolic acidosis is present, or PaCO$_2$ greater than 50 mm Hg if bicarbonate levels are normal, and 5) PaO$_2$ less than 80 mm Hg on 40% O$_2$, or a PaO$_2$ less than 200 mm Hg on 100% O$_2$.

Patients in shock should be given enough oxygen during the initial resuscitation to maintain an arterial PO$_2$ of at least 80 to 100 mm Hg. Alkalosis during sepsis also adversely affects oxygen unloading at the tissues. Sepsis reduces 2,3-DPG,[21] and a higher hemoglobin may be needed to provide adequate O$_2$ availability. Alkalosis should also be corrected because each 0.1 increase in pH reduces O$_2$ availability to tissue by about 10%.[22]

Fluids

By far the most effective initial treatment for virtually all types of shock, particularly following trauma or surgery, is early and aggressive administration of fluid until cardiac filling is optimal. It is important that two — or, preferably, three — large IV catheters be inserted and fluid administration be so rapid that hypotension from hypovolemia is corrected within 15 to 30 minutes. If shock is corrected within 15 to 30 minutes in patients who require massive transfusions, the mortality rate is only 11%.[23] If the patient has an underlying disease and shock persists for more than 30 minutes, our mortality rate with massive transfusions exceeds 90%.

Types of Fluids. In severe hypovolemic shock, volume replacement is begun with 3L of *balanced electrolyte solution* given over 15 to 30 minutes. Ringer's lactate is quite adequate. The lactate in the fluid is seldom a problem. The dextro-lactate is excreted in the urine and the levo-lactate is metabolized to bicarbonate by the liver. Normal saline is also adequate, but has the theoretical problem of a relative excess of chloride, which can contribute to acidosis.

There has been much controversy on the relative benefits of *colloids* during the initial resuscitation from trauma. No study so far has answered the questions. Lucas et al, however, found that the use of large amounts of *albumin* during the first three to five days in an attempt to maintain normal plasma albumin levels significantly decreased fibrinogen clotting (FC) activity and increased prothrombin times (PT) and partial thromboplastin times (PTT). The greater the abnormalities in FC, PT, and PTT, the greater the need for postoperative transfusions.[24] More recently they have reported that reduced coagulation activity after albumin supplementation for shock is partially due to decreased levels of coagulation proteins.[25]

Some investigators, however, have continued to support the use of albumin in resuscitation. Hauser and Shoemaker reported, in a tightly controlled crossover clinical study, that resuscitation with 25% albumin was preferable to Ringer's lactate.[26] Although albumin is expensive, the authors pointed out that prompt volume expansion may reduce ICU time and "the cost of a single day in the intensive care unit is equivalent to that of 20 to 40 units of albumin."[27]

Low-molecular-weight *dextran* has been used successfully for resuscitation by many investigators. This agent can rapidly expand blood volume and may greatly improve microcirculatory blood flow.[28] There is some concern, however, that it can occasionally cause anaphylactoid reactions and may increase bleeding from large raw surfaces.

Hydroxyethyl starch (HES) has received increasing attention. HES is a 6% (isooncotic) solution in 0.9% NaCl. In one clinical study, HES successfully expanded blood volume, but significantly increased partial thromboplastin time in 64% of patients, and prolonged prothrombin time in 28%.[29] There was, however, no clinical evidence of any hemorrhagic tendencies. Several clinical studies since then have indicated that HES is as effective as albumin for expanding blood volume, and it is much less expensive.[30]

In the past, it was thought that a hemoglobin level of about 10.0 g/dL was optimal, but we have found that critically ill patients with higher hemoglobin levels, in the range of 12.5 to 14.0 g%, tend to maintain a better intravascular volume, have a lower incidence of respiratory failure, and are more likely to survive.[31] Although Shah et al[32] found that *blood* transfusions did not increase oxygen transport or venous PO_2, their patients' rates of oxygen consumptions were already much greater than normal. Our own studies have shown that patients with a reduced oxygen consumption will increase their oxygen consumption by about 8% with each unit of packed red cells administered.

Increasing quantities of *bank blood* are given as packed red blood cells. This obviously provides increased plasma and other factors for blood banks to process for component therapy. The patient transfused only with packed red cells, however, may suffer from an inadequate restoration of the plasma lost by hemorrhage.

In one study, dogs subjected to a controlled blood loss equal to 8% of their body weight exhibited significant depression in serum protein, complement factor C3, IgG, and total opsonic activity when resuscitated with packed red cells in saline.[33] In dogs resuscitated with whole blood, no such depression in serum components or activity was observed. Ideally, fresh whole blood would be available for bleeding patients who require more than four to six units of blood.

One of the main problems with massive transfusions is the increased bleeding associated with what can be rather severe thrombocytopenia. Harrigan et al[34] found that massive transfusions were associated with decreased platelet counts and aggregability for the first four postoperative days. This was thought to be due to platelet utilization and delayed megakaryocyte response. In addition, they found a rise in betathromboglobulin (BTG) and platelet factor 4 (PF4) in the early postoperative period. This presumably indicates an ongoing platelet release reaction which may improve primary hemostasis because BTG is a PGI_2 inhibitor and PF4 is an antiheparin agent. Massive autotransfusion may also be associated with platelet abnormalities.[35]

Determination of Fluid Needs. If the patient in severe shock does not respond promptly to standard fluid therapy, and the extent of the patient's continued fluid needs are not obvious clinically, an effort should be made to insert a central venous pressure (CVP) and/or a pulmonary artery wedge pressure (PAWP) catheter to measure filling pressure changes in the right and left heart, respectively.

Isolated *CVP* levels have relatively little physiologic significance, but the response of the CVP to a fluid challenge can be extremely important. The usual fluid challenge is 3 mL/kg of a balanced electrolyte given over ten minutes while monitoring the CVP constantly.

If pulse pressure rises and there is little or no rise in the CVP, further fluid should be given. If the CVP rises abruptly as fluid is given, the rate of administration should usually be decreased or the fluids stopped until the CVP returns to baseline levels.

Tahvanian et al[36] have confirmed our earlier observations that central venous blood can also be used to calculate oxygen consumption or physiologic shunting in the lungs almost as well as pulmonary artery samples, unless the cardiac output is very high or very low.

In most instances, the pumping function of the right and left ventricles is quite similar, so that *changes* in the CVP (which reflect filling pressures in the right heart) correlate fairly well with *changes* in the *PAWP* (which reflect left ventricular filling pressures). In patients with septic or cardiogenic shock, however, the CVP and PAWP may be quite disparate.

The pulmonary artery diastolic pressure should be monitored constantly. The diastolic pulmonary artery pressure is usually only 1 to 2 mm Hg higher than the pulmonary artery wedge pressure, unless there is pulmonary hypertension. If the PADP-PAWP gradient exceeds 5 mm Hg, severe underlying pulmonary hypertension is often present. Furthermore, as emphasized by Cengiz et al,[37] pulmonary artery pressure waves should be recorded on paper and the values obtained at the end of expiration used to reduce the errors caused by ventilators. Digital read-outs tend to give deceptively high values, especially when high inflation pressures are used.

Although PAWP reflects left ventricular filling to some degree, the actual end-diastolic volumes are much more important. If myocardial compliance is reduced, such as after an acute myocardial infarction, the left ventricular end-diastolic volume may be low even if the PAWP is high. Consequently changes in PAWP and PADP with a fluid challenge are much more important than absolute levels.

Use of *blood volume determinations* to guide the rate or amount of fluid administration has been advocated by some investigators. Shoemaker, in particular, has found a number of advantages to measuring blood volumes serially.[38] In addition, some derived calculations from blood volume determinations are among his best predictors of successful therapy.

Acid Base Therapy. Most acid base problems in shock will improve spontaneously if adequate ventilation and tissue perfusion are provided. However, any serious acid base abnormality that persists may interfere with cardiovascular and or cerebral function and should be corrected.

Severe metabolic acidosis (with a pH less than 7.10) that persists in spite of fluid loading should be corrected with bicarbonate. To calculate total bicarbonate deficit, the bicarbonate space is taken to be equal to about 30% of the body weight. Thus, in an averaged-size man, it takes about 100 mEq of bicarbonate to raise the pH by 0.10.

Vincent et al have confirmed the importance of arterial lactate in prognosis in shock patients.[9] They found that survivors had initially lower lactate levels than nonsurvivors (8.0 vs 13.1 mmol/L) and survivors also had reductions of lactate levels of at least 10% per hour during treatment. In nonsurvivors the lactate levels tended to rise despite aggressive therapy.

Inotropic Agents

If shock persists in spite of rapid and aggressive fluid loading, attempts should be made to improve cardiac output by using one or more agents to increase cardiac contractility. The inotropic agents used most frequently for shock include digoxin, dopamine, dobutamine, isoproterenol, epinephrine, and calcium.

Digoxin. Digitalis increases myocardial contractility in patients with congestive heart failure and decreases atrioventricular conduction, thereby slowing the heart rate in patients with atrial flutter or fibrillation. By blocking the Na-K/ATPase pump, digitalis facilitates calcium entry into myocardial cells, thereby producing an inotropic effect.[40] This inotropic effect is not dependent on a catecholamine response and, therefore, it is also effective in patients taking beta-adrenergic blocking drugs.[41]

The use of digitalis preparations is very controversial in the patient with an acute myocardial infarction.[42] Although these drugs may improve myocardial function, they can also increase the incidence and severity of arrhythmias.[43]

Dopamine. The response to dopamine varies according to the dosage used.[43,44] At doses of 1 to 3 μg/kg/min, renal blood flow and urine output often increase with little or no change in blood pressure or cardiac output. At intermediate doses of 5 to 15 μg/kg/min, blood pressure, cardiac output, stroke volume, and myocardial contractility usually increase rather substantially. Higher doses of dopamine, exceeding 30 μg/kg/min, often cause increasing vasoconstriction.

The response of the right ventricle to dopamine is often different from that of the left ventricle. Whereas left ventricular performance may be greatly increased by dopamine, the right ventricular stroke work may increase only moderately, with relatively little change in CVP.

Dobutamine. Dobutamine is an adrenergic agent thought to produce less tachycardia, less increase in myocardial oxygen consumption, and fewer arrhythmias than dopamine.[45] Dobutamine also increases the sinus-node rate and improves AV and interventricular conduction rates. Left ventricular afterload, left atrial pressure, and systemic vascular resistance are significantly lower with administration of dobutamine than dopamine.[46] However, dobutamine, because of its vasodilator properties, generally should not be given to patients who are hypotensive or have a low systemic vascular resistance. Thus, in septic shock, dopamine is usually preferable; in cardiogenic shock, dobutamine is preferred.

Isoproterenol. If the patient with shock has a slow pulse rate, isoproterenol in doses of 1 to 2 μg/min may dramatically increase blood pressure, cardiac output, and tissue perfusion.[44] If the pulse rate exceeds 120 per minute, however, it is much less likely to improve cardiac output and has a tendency to cause myocardial ischemia.[45] Consequently it is usually contraindicated in patients with an acute myocardial infarction.

Epinephrine. Epinephrine in doses of 1 to 5 μg/min can often raise blood pressure and cardiac output in individuals who have become unresponsive to large doses of dopamine and dobutamine.[46,47] Epinephrine, however, can occasionally cause dangerous tachyarrhythmias.

Calcium. Calcium ions enter the sarcoplasm of the myocardial cell from the ECF during the plateau phase of the action potential.[48] In addition, calcium ions stored in the sarcoplasmic reticulum are released and rapidly transferred to the sites of interaction of the actin and myosin filaments. Thus an adequate quantity of plasma ionized calcium is extremely important for maintaining normal cardiac function.[47] In shock patients receiving bank blood at more than 100 mL/min, the citrate in the transfusions may reduce the ionized calcium level in the blood to a point at which it impairs cardiovascular function. Consequently the Committee on Trauma of the American College of Surgeons, in its ATLS course, recommends that a gram of calcium chloride be given after every four to five units of blood in patients receiving blood at this rapid rate.

Glucose-potassium-insulin (GKI). Significant improvements in cardiac function occasionally may occur following the administration of concentrated solutions of glucose with added potassium and insulin.[48] Recommended dosage consists of 1,000 mL of saline containing 100 to 200 g of glucose, 20 to 40 mEq of potassium chloride, and 10 to 20 units of regular insulin IV given over one to four hours.

Combinations. A wide variety of combinations of inotropic and vasodilating agents, including dopamine, dobutamine, or epinephrine with nitroprusside or nitroglycerin, have been used successfully to improve tissue perfusion in severe heart failure or shock.[49,50] These combinations are particularly helpful in patients with a low cardiac output and high systemic vascular resistance.

Steroids

Small "Replacement" Doses. It has been estimated that up to six million people in the United States have a subclinical adrenal insufficiency that can be uncovered by severe trauma or sepsis.[51] Up to 15% of patients with sepsis in an ICU may not have an appropriate increase in plasma cortisol levels and will not respond adequately to ACTH.[52] Patients with adrenal insufficiency and shock or sepsis generally will die unless given exogenous corticosteroids. As a consequence, all patients with shock that is unresponsive to fluid loading and inotropic agents should be given at least 200 mg of hydrocortisone by rapid IV injection with follow-up doses as needed.[52-54]

Massive (Pharmacological) Doses. The use of massive doses of steroids in shock therapy is controversial. There are data suggesting that massive doses of glucocorticoids may be helpful in shock by preventing uncoupling of mitochondrial electron transport and oxidative phosphorylation.[55] They also seem to stabilize lysosomal and capillary membrane permeability[56] and improve cardiovas-

cular function[57] and cell metabolism.[58] Oxygen delivery to the tissues may also be improved by a shift of the oxyhemoglobin dissociation curve to the right.[59] Jacobs et al[60] found that steroids may be of benefit by reducing the excessive activation of complement that can occur with sepsis and/or shock. This may be particularly helpful in preventing ARDS after septic shock.

Hinshaw has shown in several baboon experiments that these primates can survive an LD_{100} septic shock insult if given massive steroids and antibiotics early in treatment.[61]

Schumer et al conducted the only large double-blind, prospective clinical study of the effects of massive steroids in early septic shock.[62] Mortality rate with a placebo was 40%, but it was only 11% with administration of massive steroids.

Vasopressors

In general, vasopressors should be given only as a temporary measure when there appears to be no other rapidly effective method of restoring an adequate coronary or cerebral blood flow in patients with critical stenoses of these vessels. They should generally not be administered until an adequate trial with ventilation, oxygen, fluids, acid-base correction, inotropic agents, and steroids has been made.

Dopamine in doses of 20 to 40 μg/kg/min can raise blood pressure adequately in about 80% of patients requiring drugs to correct their hypotension. Thus only a relatively small number of patients with shock may require vasopressors such as metaraminol (Aramine) or norepinephrine (Levophed). Norepinephrine by itself can cause severe, sometimes lethal, vasoconstriction.[63] A solution containing four ampules of norepinephrine (Levophed) and two ampules of phentolamine (Regitine) can raise BP with much less danger of excessive vasoconstriction.[64,65]

Phenylephrine (Neosynephrine) is often used to treat hypotension following spinal anesthesia, which is characterized by decreased mean arterial pressure and increased vascular capacitance. Butterworth et al[66] found that isoproterenol reduced vascular capacitance, resulting in a pharmacologic autotransfusion, whereas phenylephrine acted primarily by increased peripheral vascular resistance. Ephedrine effectively combined both these effects. Thus ephedrine seemed to be a more appropriate drug treatment for spinal anesthetic hypotension than was either neosynephrine or isoproterenol.

Vasodilators

If the patient shows evidence of excessive vasoconstriction and poor tissue perfusion in spite of all other therapy, and if his blood pressure is normal or high, a vasodilator may be very helpful. A vasodilator should not be used, however, in patients who are hypovolemic. Vasodilators in full dosage may increase vascular capacity by as much as 2 to 3 L,[67] further accentuating the hypovolemia and causing sudden severe hypotension. The use of vasodilators may also be dangerous in patients who are already vasodilated and have a low systemic vascular resistance.[68]

Nitroprusside is administered by continuous IV infusion, usually in doses of 0.5 to 3.0 μg/kg/min. This drug causes a reduction in afterload.[69] A PAWP of 15 to 18 mm Hg and a systolic arterial pressure of at least 80 to 90 mm Hg should be maintained, if possible, before and during the administration of the nitroprusside.

Nitroglycerin is also effective as a vasodilator.[70] It dilates coronary and systemic arteries in doses similar to nitroprusside. It also has an even more pronounced effect on veins, however, so that its main effect is to reduce preload.[71]

Diuretics

If the urine output is less than 0.5 mL/kg/h despite adequate fluids and adequate blood pressure, 12.5 to 25.0 g of mannitol may be infused IV over a period of 10 to 20 minutes with a similar dose every one to four hours as needed.[72] If the urine output is still inadequate, furosemide (Lasix) can be given.[73]

Antibiotics

Antibiotics should be started at the earliest indication of any infection or contamination, after appropriate smears and cultures have been obtained. Altemeier et al have shown, in a large series of septic patients, that the mortality rate of sepsis was much higher (54%) when the patient was given an inappropriate antibiotic than when an appropriate antibiotic, chosen on the basis of culture sensitivities, was used (28%).[74]

Bactericidal or bacteriostatic agents can be equally effective in gram-negative infections.[75] The patterns of susceptibility vary widely from hospital to hospital, but certain general recommendations may be made. Treatment is started with one of the aminoglycosides (tobramycin or gentamicin) to cover the usual gram-negative aerobes. When cultures and susceptibility tests become available, a less toxic, but effective, drug should be substituted. If gram-positive cocci are seen on smear, a synthetic penicillin should be used. In anaerobic infections, such as necrotizing fasciitis, the smear frequently shows pleomorphic gram-negative bacilli (Bacteroides) and a mixture of aerobes and anaerobes. Thus a three-drug regimen is used frequently in severe abdominal sepsis, comprising 10 to 20 million units of penicillin G, 2,400 mg of clindamycin, and 5 mg/kg/day of gentamicin. In severe gram-negative sepsis, peak blood levels for gentamicin and tobramycin should be 8 to 10 μg/mL.[76,77] This usually requires a dose of 2.0 to 2.5 mg/kg. With such doses, the interdose interval may have to be 16 to 24 hours to obtain trough levels below 1.0 μg/mL.[78]

Heparin

Although there is controversy regarding the value of heparin for the treatment of DIC,[79] we recommend that it be started if serial coagulation studies reveal DIC without fibrinolysis. This situation is indicated by a progressive reduction in the platelet count and fibrinogen levels without an increase in fibrin split products (FSP). Under such circumstances, intravascular clots may form without enough fibrinolysis to keep the microcirculation open.

Mechanical Assistance

Military Antishock Trousers (MAST). Although the MAST garment is now being used with enthusiasm in many parts of the country to help treat hemorrhagic shock en route to the hospital,[80] many physicians remain skeptical of its value. Although it was originally thought that the MAST garment caused an autotransfusion of 700 to 1,000 mL of blood, more recent studies suggest that it actually raises BP primarily by increasing afterload[81] and reducing perfusion of tissues covered by MAST. In addition, McCabe et al[82] showed

that MAST can cause a 14% decrease in pulmonary vital capacity. This may be a critical factor in patients with respiratory insufficiency.

Intraaortic Balloon Pumping (IABP). Cardiogenic shock frequently persists in spite of adequate ventilation, oxygen, fluids, acid-base correction, inotropic agents, steroids, vasopressors or vasodilators, and control of arrhythmias. This persistent cardiogenic shock is caused by "power failure" because of inadequate functioning of 35% to 40% or more of the left ventricular myocardium.[83,84] If shock from myocardial failure persists for more than two hours, the mortality rate approaches 100%.[85] Consequently mechanical support of the circulation by IABP, which reduces systolic blood pressure and increases diastolic aortic pressure, may greatly improve coronary blood flow relative to myocardial O_2 needs.[86]

Newer Agents

Naloxone (Anti-endorphin) Therapy. Beta endorphins are endogenous opiates secreted by the same cells in the hypothalamus that secrete ACTH. Hence any stimulus such as shock which causes ACTH release will also cause beta-endorphin release.[87] These opiates apparently cause hypotension primarily by lowering peripheral vascular resistance, but they may also cause myocardial depression.[88] Although naloxone has little or no effect on the cardiovascular system of normal animals, it may increase arterial blood pressure and survival in many animals with endotoxin-induced hypotension.[89] The mechanism of action is thought to be a central inhibition of opioid receptors. Although the increased peripheral resistance represents the sum total of naloxone's effect, it may have varying effects on different vascular beds.[90] Vernese et al[91] showed that naloxone is a vasodilator of canine muscular arteries, probably by a direct effect on the vessel.

The results obtained clinically with naloxone have not been as good as those seen in experimental animals, possibly because of late administration and the much smaller doses used in patients. Rock et al[92] used increasing doses of naloxone (0.1, 0.2, 0.4, 0.8, 1.6 mg/kg) in 12 patients with septic shock, and they found an increase in mean arterial BP greater than 10 mm Hg in only four patients. In addition, four patients developed adverse reactions (hypotension in two, pulmonary edema in one, and grand mal seizures in one).

Prostaglandins. Prostaglandins are a large family of naturally occurring lipids formed from arachidonic acid by metabolism initiated by the enzyme cyclooxygenase. Several studies have shown that a number of these substances, including thromboxane (TXA_2) and prostacyclin (PGI_2), are elevated in septic shock. Although some of these prostaglandins, such as thromboxane, may be harmful in shock, others, such as PGE_1 and prostacyclin, can be helpful. For example, PGE_1 has been used with benefit in experimental hemorrhagic shock by at least two groups of investigators.[93,94] Its main effects have been a decrease in peripheral resistance and an increase in cardiac output and blood pressure. PGI_2 (prostacyclin) has received much attention because of its ability to cause vasodilation and inhibit platelet aggregation.[95] Studies on lethal endotoxemia in dogs have shown that PGI_2 can improve tissue perfusion and organ function.[96,97]

Prostaglandin inhibitors also have received wide attention. For example, the changes in intracortical renal blood flow after *Escherichia coli* bacteremia are associated with an increase in prostaglandin levels and are prevented by pretreatment with indomethacin (a cyclooxygenase inhibitor).[98] Loe and Bowen studied *E coli* sepsis in a canine model that was pretreated with a thromboxane synthetase inhibitor.[99] Surgery and sepsis caused a significant increase in the TxB_2 (a stable metabolite of thomboxane A_2) over baseline values, and this increase was completely prevented by treatment with the Tx synthetase inhibitor. Inhibition of Tx synthesis also tended to improve total peripheral resistance, intracellular oxygen tension, and transmembrane potential differences.

Studies by Reines et al[100] found that central venous plasma levels of thromboxane in eight patients dying of septic shock were more than tenfold higher than in survivors. These data suggest that treatment with imidizole, an inhibitor of thromboxane synthetase, might be beneficial in septic shock.[101]

Adenosine Triphosphate (ATP) Administration. For many years there has been interest in various methods of improving cell metabolism and raising intracellular levels of ATP. It has generally been assumed that exogenously administered ATP cannot enter cells; however, Chaudry and his coworkers have shown that even under normal conditions, some ATP can enter muscle cells, and that this amount is increased during shock.[102] It was also found that a glucose ATP-$MgCl_2$ mixture significantly increased survival in rats who had peritonitis due to cecal ligation.

Chaudry et al[103] also have investigated the pharmacologic safety of administering adenosine triphosphate-magnesium chloride in normal man. Their study confirmed that ATP-$MgCl_2$ is a potent vasodilator, and they also found an increased cardiac output in proportion to the decrease in peripheral resistance caused by ATP.

Unfortunately there may be problems with ATP infusions. Horton et al[104] found that although the use of ATP-$MgCl_2$ in canine hemorrhagic shock increased coronary blood-flow and oxygen delivery, there was a progressive decrease in cardiac performance. The decrease in myocardial oxygen extraction, together with a negative lactate balance in the myocardium, suggest that a metabolic defect developed in the animals receiving ATP-$MgCl_2$.

Antisera. The use of antiserum to endotoxin has recently been investigated by Ziegler et al[105] in a prospective study of 212 patients with gram-negative sepsis. Antiserum produced from the J-5 mutant strain of *E coli*, which contains only core determinants, was used. The mortality rate of the control group was 39%, compared to 22% in the antiserum group. The effect in those with profound shock was even greater, with mortality rates of 77% in the control group compared to 44% in the treated group. Although not currently available to practitioners, such antisera may play a significant role in the management of gram-negative bacteremia in the future.

Calcium Blockers. A number of calcium-channel blockers have been shown to have beneficial effects on myocardium,[106] brain,[107] and kidney[108] after ischemia. While these agents have received wide attention in experimental organ preservation, their value in clinical situations is unclear.

Although calcium blockers may be

helpful in maintaining viability of ischemic organs, they also may interfere with efforts to maintain blood pressure and cardiac output during resuscitation. Denis et al[109] found that, in dogs subjected to hemorrhagic shock, a prior total parathyroidectomy or use of a calcium blocker (Verapamil) greatly impaired the dogs' normal homeostatic response to shock. Augmentation of the intact parathyroid response to postshock hypocalcemia by giving calcium seemed to improve the acute cardiovascular response.

REVERSIBLE CAUSES OF "IRREVERSIBLE" SHOCK

Some of the more frequently overlooked, treatable causes of persistent shock include inadequate infusion of fluids, inadequate ventilation, unrecognized pneumothorax, pulmonary emboli, inadequately treated sepsis, cardiac tamponade, acid-base or electrolyte abnormalities, adrenal insufficiency, hypothermia, and previous prolonged treatment with antihypertensive drugs.

A specific search for these entities should be made before considering the patient incurable.

SUMMARY & CONCLUSIONS

In spite of all the scientific and technical advances in recent years, shock that is not rapidly correctable with fluid can have a morbidity rate exceeding 80%. Consequently awareness of such precipitating factors as sepsis and early diagnosis and treatment are essential.

Treatment should be rapid and should follow a previously outlined protocol. Such protocols should include correction of the precipitating problem and aggressive resuscitation to assure adequate ventilation and oxygenation of the blood and optimal oxygen delivery to the tissues. Fluid and blood should be given as needed until filling pressures begin to rise rapidly with further fluid infusion. With hemorrhagic shock in previously healthy individuals, a hemoglobin level of 10.0 g dL is usually adequate. In older, septic, or cardiogenic shock patients, a hemoglobin level of 12.5 to 14.0 may be preferable.

If an optimal preload does not increase cardiac output to normal or higher levels, inotropic agents should be used. If shock still persists, one must be sure that the arterial pH is not excessively high or low. Glucocorticoids may then be given in low dose (200 mg hydrocortisone) in case some degree of adrenal insufficiency is present. They can also be given in high doses (equivalent to 150 mg/kg hydrocortisone) early in septic shock primarily to prevent excess complement activation and to preserve membrane integrity.

Vasopressors may occasionally be required if there is excessive vasodilation, especially if there is persistent hypotension in the presence of high-grade coronary or cerebral artery stenosis. Vasodilators may be used to try to correct myocardial ischemia (nitroglycerin), excessive preload (nitroglycerin), or excessive afterload (nitroprusside or hydralazine). Combinations of vasodilators and inotropic agents may be required in some patients with high systemic vascular resistance and persistently low cardiac outputs. Mechanical assist with IABP can be of great value in persistent cardiogenic shock.

Diuretics may occasionally help prevent renal failure in patients who are persistently oliguric after blood flow and pressure are restored. Heparin is occasionally of value if DIC develops with no concomitant fibrinolysis. Antibiotics are important in septic shock and may also be important if persistent shock has reduced gastrointestinal mucosal integrity so that bacteria and bacterial products can enter the portal system.

Newer studies have focused on naloxone (which can usually raise BP in experimental shock, but is of questionable clinical value), prostaglandins (which include a myriad of substances with various effects), prostaglandin inhibitors, and ATP-$MgCl_2$ (so far studied seriously by only one group). The most exciting newer substances include calcium-channel blockers and antisera to endotoxin. These latter two agents could conceivably revolutionize resuscitation and the treatment of septic shock.

REFERENCES

1. Wilson RF, Thal AP, Kindling PH, et al: Hemodynamic measurements in septic shock. *Arch Surg* 1965;91:121-129.

2. MacLean LD, Mulligan WG, McLean APN, et al: Patterns of septic shock in man: A detailed study of 56 patients. *Ann Surg* 1967;166:543.

3. Mackenzie GJ, Taylor SH, Flenley DC, et al: Circulatory and respiratory studies in myocardial infarction and cardiogenic shock. *Lancet* 1964;2:825.

4. Ascanio G, Borrera F, Lantsh EV, et al: Role of reflexes following myocardial necrosis. *Am J Physiol* 1965;209:1081.

5. Chien S: Role of the sympathetic nervous system in hemorrhage. *Physiol Rev* 1967;47:214.

6. Green HD, Rapela CD: Neurogenic and autoregulation of the resistance and capacitance components of the peripheral vascular system in shock and hypotension, in Mills LC, Moyer JH (eds): *Pathogenesis and Treatment*. New York, Grune & Stratton, 1965, pp 91-110.

7. Rector JB, Stein JH, Bay WH, et al: Effect of hemorrhage and vasopressor agents on distribution of renal blood flow. *Am J Physiol* 1972;222:1125.

8. Skillman JJ, Lawler RP, Hickler RB, et al: Hemorrhage in normal man: Effect of renin, cortisol, aldosterone and urine composition. *Ann Surg* 1967;166:865.

9. Vincent JL, Dufaye P, Berde J, et al: Serum lactate determinations during circulatory shock. *Crit Care Med* 1983;11:449-451.

10. Wilson RF, Krome RL: Factors affecting prognosis in clinical shock. *Ann Surg* 1969;169:93-101.

11. Bleich HL, Schwartz WB: Tris buffer (THAM). An appraisal of its physiological effects and clinical usefulness. *N Engl J Med* 1966;274:782.

12. Wilson RF, Gibson DB: The use of arterio-central venous oxygen differences to calculate cardiac output and oxygen consumption in critically ill surgical patients. *Surgery* 1978;84:362-369.

13. Wilson RF, Chiscano A, Quadros E, et al: Some observations on 132 patients with septic shock. *Anesth Analg* 1967;46:751-763.

14. McCabe WR, Jackson GG: Gram-negative bacteremia. *Arch Intern Med* 1962;110:847.

15. Freid MA, Vosti KL: The importance of underlying disease in patients with gram-negative bacteremia. *Arch Intern Med* 1968;121:418.

16. Burke JF, Pontoppidan H, Welch CE: High output respiratory failure. An important cause of death ascribed to peritonitis or ileus. *Ann Surg* 1963;158:581.

17. Wilson RF, McCarthy B, LeBlanc LP, et al: Respiratory and coagulation changes after uncomplicated fractures. *Arch Surg* 1973;106:395.

18. Wilson RF, Antontnko D, Gibson DB: Shock and acute respiratory failure after chest trauma. *J Trauma* 1977;17:697-705.

19. Aubier M, Viires N, Syllie G, et al: Respiratory muscle contribution to lactic acidosis in low cardiac output. *Am Rev*

Resp Dis 1982;126:648-52.

20. Wilson RF, Kati A, Asuncion Z, et al: Clinical respiratory failure after shock or trauma: Prognosis and methods of diagnosis. *Arch Surg* 1969;98:538-550.

21. McConn R, Del Guercio LRM: Respiratory function of blood in the acutely ill patient and the effect of steroids. *Ann Surg* 1970;174:436.

22. Bryan-Brown CW, Back SM, Makabali G, et al: Consumable oxygen availability in relation to oxyhemoglobin dissociation. *Crit Care Med* 1963;1:17.

23. Wilson RF, Mammen E, Walt AJ: Eight years of experience with massive blood transfusions. *J Trauma* 1971;11:275-285.

24. Johnson SD, Lucas CE, Gerrick SI, et al: Altered coagulation after albumin supplements for treatment of oligemic shock. *Arch Surg* 1979;114:379-383.

25. Lucas CE, Bouwman DL, Ledgerwood AM, et al: Differential serum protein changes following supplemental albumin resuscitation of hypovolemic shock. *J Trauma* 1980;20:47-51.

26. Shoemaker WC, Schluchter M, Hopkins JA, et al: Comparison of the relative effectiveness of colloids and crystalloids *in emergency resuscitation*. *Am J Surg* 1981;142:73.

27. Hauser CJ, Shoemaker WC: Albumin resuscitation for shock, letter. *Surgery* 1980;88:183-184.

28. Shoemaker WC: *Comparison of the* relative effectiveness of whole blood transfusions and various types of fluid therapy in resuscitation. *Crit Care Med* 1976;4:71-78.

29. Lee WH Jr, Cooper N, Weedner MG Jr, et al: Clinical evaluation of a new plasma expander, hydroxyethyl starch. *J Trauma* 1968;8:381.

30. Puri VK, Pandipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia in shock. *Crit Care Med* 1981;9:833-837.

31. Wilson RF, Gibson DB: The use of arteno central venous oxygen differences to calculate cardiac output and oxygen consumption *in* critically ill surgical patients. *Surgery* 1978;84:362.

32. Shah DM, Gottlieb ME, Rahm RL, et al: Failure of red blood cell transfusion to increase oxygen transport or mixed venous PO_2 in injured patients. *J Trauma* 1982;22:741-746.

33. Berting CV, Kocak KI, Dritter RL, et al: Whole blood vs packed red cells for resuscitation of hemorrhagic shock: An examination of host defense parameters in dogs. *Surgery* 1978;84:494.

34. Harrigan C, Mammen EF, Ledgerwood AM: Altered platelet function and proteins after hypovolemic shock. *Surg Forum* 1983;34:10-12.

35. Moore EE, Dunn EL, Breslich DJ, et al: Platelet abnormalities with massive autotransfusion. *J Trauma* 1981;20:1052-1056.

36. Tahvanainen J, Meretoja O, Nikki P: Can central venous blood replace mixed venous blood samples? *Crit Care Med* 1982;10:758-761.

37. Cengiz M, Crapo RO, Gardner RM: The effect of ventilation on the accuracy of pulmonary artery and wedge pressure measurements. *Crit Care Med* 1983;11:502-507.

38. Shoemaker WC, Monson DO: Effect of whole blood and plasma expanders on volume-flow relationships in critically ill patients. *Surg Gynecol Obstet* 1973;137:453.

39. Shoemaker WC, Czer LSC: Evaluation of the biologic importance of various hemodynamic and oxygen transport variables. *Crit Care Med* 1979;7:424.

40. Moe GK, Farah AE: Digitalis and allied cardiac glycosides, in Goodman LS, Gilman A (eds): The pharmacologic basis of therapeutics. New York, MacMillan, 1975, pp 653-682.

41. Fawaz G: Effect of reserpine and pronethalol on the therapeutic and toxic actions of digitalis on the dog heart preparation. *Br J Pharmacol* 1967;29:302.

42. Gunnar RM, Loeb HS, Pietras RJ, et al: The hemodynamic effects of myocardial infarction and results of therapy. *Med Clin North Am* 1970;54:253.

43. Goldberg LI: Dopamine — Clinical use of an endogenous catecholamine. *N Engl J Med* 1974;291:707.

44. Wilson RF, Sibbald WJ, Jaanimagi JL: Hemodynamic effects of dopamine in critically ill septic patients. *J Surg Res* 1976;20:163.

45. Sonnenblick EH, Frishman WH, LeJemtel TH: Dobutamine: A new synthetic cardioactive sympathetic amine. *N Engl J Med* 1979;300:17.

46. DiSesa V, Brown E, Mudge G, et al: Clinical comparison of dopamine and dobutamine in postoperative cardiac patients. *Surg Forum* 1980;31:266.

47. Niedergerke R: The rate of action of calcium ions on the contraction of the heart. *J Physiol* 1957;138:506.

48. Moffitt EA, Molnar GD, Pluth JR, Et al: Effects on metabolism and cardiac output of glucose potassium solution with and without insulin. *Ann Thorac Surg* 1973;15:1.

49. Herbert P, Tinker J: Inotropic drugs in acute circulatory failure. *Intens Care Med* 1979;91:229.

50. Miller RR, Palamo J, Brandon JA, et al: Combined vasodilator and inotropic therapy of heart failure: experimental and clinical concepts. *Am Heart J* 1981;102:500.

51. Melby JC: Systemic corticosteroid therapy: Pharmacology and endocrinologic considerations. *Ann Intern Med* 1974;81:505.

52. Sibbald WJ, Short A, Cohen MP, et al: Variations in adrenocortical responsiveness during severe bacterial infections. *Ann Surg* 1977;186:29.

53. Chernow B: Hormonal and metabolic considerations in critical care medicine in *Critical Care: State of the Art*. Fullerton, California: Society of Critical Care Medicine, 1982, vol 3, p 11.

54. Reichgott MJ, Melman KL: Should corticosteroids be used in shock? Symposium on steroid therapy. *Med Clin North Am* 1973;57:1211.

55. DePalma RG, Gluckman MH, Hartman P, et al: Prevention of endotoxin induced changes in oxidative phosphorylation in hepatic mitochondria. *Surgery* 1977;82:67.

56. Sibbald WJ, Anderson RR, Reid B, et al: Alveolar capillary permeability in human septic ARDS: Effect of high dose corticosteroid therapy. *Chest* 1981;79:133.

57. Altura BM, Altura BT: Peripheral vascular actions of glucocorticoids and their relationship to protection in circulatory shock. *J Pharmacol Exp Ther* 1976;190:300.

58. Hinshaw LB, Archer LT, Black MR, et al: Effects of methylprednisolone sodium succinate on myocardial performance, hemodynamics, and metabolism in normal and failing hearts, in Glenn TM (ed): *Steroids and Shock*. Baltimore: University Park Press, 1974.

59. Bryan-Brown CS, Back SM, Makabali G, et al: Consumable oxygen: Study of oxygen availability in relation to oxyhemoglobin dissociation. *Crit Care Med* 1973;1:26.

60. Jacob HS: Complement induced vascular leukostasis. *Arch Pathol Lab Med* 1980;104:617.

61. Hinshaw LB, Archer LT, Kelly E, Bell BK, et al: Survival of primates in LD_{100} septic shock following therapy. *J Surg Res* 1980;[illegible].

62. Schumer W: Steroids in the treatment of clinical septic shock. *Ann Surg* 1976;184:333.

63. McKay DG, Whitaker AN, Cruse V: Studies of catecholamine shock. *Am J Physiol* 1969;56:177.

64. Chien S: Role of sympathetic nervous system in hemorrhage. *Physiol Rev* 1967;47:214.

65. Wilson RF, Sarver EJ, Rue LJ: Hemo-

dynamic changes, treatment and prognosis in clinical shock. *Arch Surg* 1971;102:21-24.

66. Butterworth JF, Prestone W, Berrizbeitia LD, et al: Pharmacologic "autotransfusion" after total spinal anesthesia. *Surg Forum* 1984;35:1-3.

67. Fromm S, Wilson RF: Phenoxybenzamine in human shock. *Surg Gynecol Obstet* 1969;129:789-763.

68. Fromm S, Wilson RF: Phenoxybenzamine in human shock. *Surg Gynecol Obstet* 1969;121:789.

69. Parmely WW, Chatterjee K, Charuzi Y: Hemodynamic effects of noninvasive systolic unloading (nitroprusside) and diastolic augmentation (external counterpulsation) in patients with acute myocardial infarction. *Am J Cardiol* 1974;33:819.

70. Avers SM: Ventricular function, in Shoemaker WC, Thompson WL (eds): *Critical Care: State of the Art*. Fullerton, California, Society of Critical Care Medicine, 1980, p 22.

71. Ludbrook PA, Byrne JD, Kurnik PB, et al: Influence of reduction of pre-load and afterload by nitroglycerin on left ventricular diastolic pressure volume relations and relaxation in man. *Circulation* 1977;56:937.

72. Warren SE, Blantz RC: Mannitol. *Arch Intern Med* 1981;141:493.

73. Levin NW: Furosemide and ethacrynic acid in renal insufficiency. *Med Clin North Am* 1971;55:107.

74. Altemier WA, Todd JC, Wellford WI: Gram negative septicemia: A growing threat. *Ann Surg* 1967;166:530.

75. Altemeier WA, Todd JC, Wellford WI: Gram negative septicemia: A growing threat. *Ann Surg* 1967;166:530.

76. MacLean LD: Shock: Causes and management of circulatory collapse, in Sabiston DC Jr (ed): *Textbook of Surgery*. Philadelphia, WB Saunders, 1981, p 87.

77. Hull J, Sarubbi F: Gentamicin serum concentrations: Pharmacokinetic predictions. *Ann Intern Med* 1976;77:657.

78. Dahlgen G, Anderson EJ, Hewitt WI: Gentamicin blood levels: A guide to nephrotoxicity. *Antimicrob Agents Chemother* 1975;8:58.

79. Carrigan JJ Jr, Jordan CM, Bennett BB: Disseminated intravascular coagulation in septic shock. *Am J Dis Child* 1973;126:629.

80. McSwain NE: Pneumatic trousers and the management of shock. *J Trauma* 1977;17:719.

81. Gattney EA, Thal ER: Hemodynamic effects of medical anti-shock trousers (MAST garment). *J Trauma* 1981;21:931-937.

82. McCabe JB, Seidel DR, Jagger JA: Antishock-trouser inflation and pulmonary vital capacity. *Ann Emerg Med* 1983;12:290-293.

83. Harnarayan C, Bennett MA, Pentecost BL, et al: Quantitative study of infarcted myocardium in cardiogenic shock. *Br Heart J* 1970;32:728.

84. Page DL, Canfield JB, Kastor JA, et al: Myocardial changes associated with cardiogenic shock. *N Engl J Med* 1971;285:133.

85. Bregman D, Parodien M Jr: Left ventricular and undirectional intra-aortic balloon pumping. *J Thorac Cardiovasc Surg* 1974;68:677.

86. Buckley MJ, Austen WG, Gold HK, et al: Intraaortic balloon assis for cardiogenic shock and ischemic states at Massachusetts General Hospital. *Med Instrum* 1976;10:253.

87. Guillemin R, Vargo T, Rossier J, et al: Beta-endorphin and adreno corticotropin are secreted concomitantly by the pituitary gland. *Science* 1977;197:1367.

88. Gurll NJ, Lechner R, Vargish T, et al: Endorphins and opiate receptors are involved in myocardial depression of canine hemorrhagic shock. *Clin Res* 1980;28:8A.

89. Reynolds DG, Gurll NJ, Vargish T, et al: Blockade of opiate receptors with naloxone improves survival and cardiac performance in canine endotoxic shock. *Circ Shock* 1980;7:29.

90. Albert SA, Shires GJ III, Illner H, et al: Effects of naloxone in hemorrhagic shock. *Surg Gynecol Obstet* 1982;155:326-332.

91. Vernes NA, Suval W, Machiedo GW, et al: Naloxone: A vasodilator in canine gracilis muscle. *Surg Forum* 1983;34:3-5.

92. Rock P, Silverman H, Plump D, et al: Efficacy and safety of Naloxone in septic shock. *Crit Care Med* 1988;13:28-33.

93. Hissen W, Fleming JS, Bierwagen ME, et al: Effect of prostaglandin E on platelet aggregation in vitro and in hemorrhagic shock. *Microvasc Res* 1969;1:374.

94. Machiedo GW, Brown CS, Lavigne JE, et al: Beneficial effect of prostaglandin E in experimental hemorrhagic shock. *Surg Gynecol Obstet* 1976;143:333.

95. Fletcher JR, Ramwell PW: The effects of prostacyclin (PGI2) on endotoxin shock and endotoxin-induced platelet aggregation in dogs. *Circ Shock* 1980;7:29.

96. Drausz MM, Utsunomiya T, Fuerstein G, et al: Reversal of lethal endotoxemia with prostacyclin. *Surg Forum* 1980;31:89.

97. Leter AM, Tabas J, Smith EF III: Salutary effects of prostacyclin endotoxic shock. *Pharmacology* 1980;21:206.

98. Stone AM, Chardavoyne R, Steing TA, et al: Intrarenal blood flow changes of sepsis — a prostaglandin effect. *Surg Forum* 1980;31:65.

99. Loe WA Jr, Bowen JC: Thromboxane synthetase inhibition during septic shock. *Surg Forum* 1984;35:3-5.

100. Reines HD, Halushka PV, Cook JA, et al: Intrarenal blood flow levels are raised in patients dying with septic shock. *Lancet* 1982;2:174-175.

101. Smith EF III, Tabas JH, Leter AM: Beneficial actions of imidizole in endotoxin shock. *Prostaglandins Med* 1980;4:215.

102. Hirasawa H, Chaudhry IH, Baue AE: Beneficial effect of ATP-MgCl2 glucose administration on survival following sepsis. *Surg Forum* 1978;29:11.

103. Chaudhry IH, Keeter JR, Barash P, et al: ATP-CL2 infusion in man: Increased cardiac output without adverse systemic hemodynamic effects. *Surg Forum* 1984;35:14-16.

104. Horton JW, Landreneau RJ, Coln D: Cardiovascular effects of ATP MgCl2 in hemorrhagic shock. *Surg Forum* 1983;34:15-17.

105. Ziegler EJ, McCutchan A, Fierer J, et al: Treatment of gram negative bacteremia and shock with human antiserum to a mutant Escherichia coli. *N Engl J Med* 1982;307:1225-1228.

106. Naylor QWB, Ferrari R, Williams A: Protective effect of pretreatment with verapamil, nifedipine and propranolol on myocardium. *Am J Cardiol* 1980;46:242-248.

107. White BC, Winegar CO, Wilson RF, et al: Calcium blockers in cerebral resuscitation (abstract). 42nd Annual Meeting Am Assoc Surg Trauma, Colorado Springs, 1982. *J Trauma* 1983;23:778-794.

108. Watt RB, White G, David JH: Beneficial effects of verapamil on postischemic renal failure. *Surgery* 1983;94:276-282.

109. Dawe DR, Lucas CE: Calcium resuscitation from shock in eupara thyroid and hypoparathyroid dogs. *Surg Forum* 1983;34:66-68.

SPECIAL CONTRIBUTION
Adult respiratory distress syndrome; complement; iron;
leukocytes; oxygen radicals

Current Concepts Regarding Adult Respiratory Distress Syndrome

Peter A Ward MD
Kent J Johnson MD
Gerd O Till MD
Ann Arbor Michigan

From the Department of Pathology, The University of Michigan, Ann Arbor, Michigan

Presented at the 1985 UAEM/IREM Research Symposium in Orlando, Florida, February 7-8, 1985

Supported in part by NIH grants GM29507, GM28499, HL28442, and HL31963

Address for reprints: Peter A Ward, MD, Department of Pathology, The University of Michigan Medical School, Box 045, M5240 Medical Science I, 1315 Catherine Road, Ann Arbor, Michigan 48109-0054

Adult respiratory distress syndrome (ARDS) is a multietiologic acute and progressive pulmonary dysfunction that may be precipitated by any of a number of pathogenic agents. Clinical and experimental studies suggest that activation of complement and blood neutrophils plays a significant role in the development of pulmonary vascular injury, which is an important pathophysiological feature of ARDS. Although the specific cellular and biochemical mechanisms resulting in the development of ARDS are unknown, it has been suggested that oxygen-derived free radicals generated from complement-activated granulocytes may be involved, directly or indirectly, in the destruction of lung vascular endothelium and alveolar tissue matrix. This hypothesis is supported by recent experimental studies showing that acute lung injury secondary to systemic complement activation can largely be prevented by interventions that scavenge for hydroxyl radicals or restrict availability of ionic iron. [Ward PA, Johnson KJ, Till GO: Current concepts regarding adult respiratory distress syndrome. Ann Emerg Med August 1985;14:724-728.]

Introduction

During the past decade, the term adult respiratory distress syndrome (ARDS) has been synonymous with acute respiratory syndrome, shock lung, wet lung, and so forth. Although it had been known for some time that sudden deterioration of lung function and oxygenation was associated with the so-called "white out" of lung as demonstrated by radiography, it became increasingly apparent during the years of the American involvement in the Vietnam War that, in patients with shock or trauma, the shock lung syndrome, or ARDS, had clinical features that could be broadly categorized into a syndrome complex. It also became obvious that no single etiologic agent is associated with the development of ARDS, and that sepsis is the cause in less than half of the cases. ARDS is a rapidly progressive disorder with a mortality rate approaching 50% within the first three days, whose survivors demonstrate a significant degree of permanent pulmonary changes, including some evidence of interstitial fibrosis.[1-7]

The generally accepted criteria for the diagnosis of ARDS are shown (Figure 1). The syndrome is associated with rapid and progressive onset of respiratory failure, and it can be distinguished from respiratory difficulties in patients who have preexisting obstructive lung disease. In ARDS there is radiographic evidence of diffuse, bilateral lung densities. There is no evidence of elevation in the capillary wedge pressure, an important criterion, because increased capillary hydrostatic pressure due to left heart failure would itself produce pulmonary edema, which behaves differently than ARDS. Another criterion is that arterial oxygen pressure drops in association with a refractory hypoxemia that cannot be corrected by the administration of 100% oxygen. These are the criteria that are generally accepted for the inclusion of patients into a classification of ARDS.

ARDS is associated with many different underlying medical problems, including shock, sepsis, nonpulmonary trauma, viral pneumonia, smoke inhalation, burn injury to the skin, cardiopulmonary bypass, and others. Clearly there is no single primary etiology that can be incriminated in the development of ARDS.

On the other hand, there is some evidence that the development of ARDS

may be associated with complement activation and neutrophil actions. This (tentative) conclusion is based on a great number of clinical observations (Figure 2). First, there is evidence that in ARDS there are increased numbers of leukocytes within the lung.[8] Infusion of indium-labeled neutrophils demonstrates a much greater degree of neutrophil localization within the pulmonary vascular system of patients with ARDS than in non-ARDS individuals.[8] In addition, it has been demonstrated that bronchoalveolar lavage fluid from the lungs of ARDS patients has an increased number of neutrophils as compared to that of control patients, in whom the number of neutrophils rarely exceeds 4% of total cells.[9]

There is evidence for the presence of activated neutrophils in the blood of patients with ARDS.[10] Blood neutrophils obtained from these patients show increased chemotactic activity in vitro, as well as the ability to generate oxygen-derived free radicals.[10] There are also increased levels of lactoferrin in the plasma of ARDS patients,[11] which suggests that activation of neutrophils and secretion of lactoferrin has occurred somewhere within the vascular system.

ARDS patients also show evidence of complement activation, as demonstrated by alternative complement pathway changes,[12] as well as the presence of a leukocyte-aggregating factor with the features of the peptide from the fifth component of complement, C5a anaphylatoxin.[13] Additionally, it has been reported that in patients with ARDS, the α 1-antiproteinase obtainable by bronchoalveolar lavage fluid is in a state of chemical inactivation due to oxidative changes in a methionyl residue of this protein,[14,15] although neutrophil-dependent oxidation was not specifically implicated.

These data suggest that in ARDS there is evidence of neutrophil activation as well as evidence of activation of the complement system. Moreover, these findings may be relevant to the pulmonary dysfunction and the evidence of inactivated α 1-antiproteinase in the lungs of ARDS patients. These findings do not imply that some of the same observations might not be made in non-ARDS patients. It is quite possible, for instance, that some of the same features could be associated with endotoxemia. In general, however, the constellation of findings tends to support the hypothesis that complement activation leads to stimulation of neutrophils, which in turn is associated with oxygen radical generation leading to lung injury.

Fig. 1. *Generally accepted criteria for ARDS.*

1. Rapid onset and progression of respiratory dysfunction
2. Diffuse bilateral lung densities by radiograph
3. No elevation in capillary wedge pressure
4. Decreased arterial blood oxygen pressure
5. Refractory hypoxemia

Complement, Neutrophils & Oxygen Radicals

The most convincing experimental evidence that complement activation can lead to acute lung injury comes from experiments performed on rats. Intravenous infusion of the potent complement-activating agent isolated from cobra venom resulted in the prompt appearance of a chemotactic peptide in the plasma of these animals. This was accompanied by evidence of neutrophil aggregation and sequestration within the pulmonary interstitial capillary network, endothelial cell damage or destruction, and interstitial and intra-alveolar edema, hemorrhage, and fibrin deposition.[16] Damage to the lung was shown to be dependent on the availability of the complement system and the presence of neutrophils. Lung injury could be blocked by treatment of the animals with catalase, which destroys hydrogen peroxide (H_2O_2).[16]

More recently accumulated evidence has shown that, in fact, a conversion product of H_2O_2 is involved, namely the hydroxyl radical ($HO^{\cdot}$).[17] This highly reactive and toxic oxygen radical is thought to be formed through the Fenton reaction, as follows:

$$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + HO^{\cdot} + OH^{-}$$

In this process, iron is oxidized to its ferric (Fe^{+++}) state. It is thought that the hydroxyl radical is the main culprit in endothelial cell damage in this model of acute lung injury. Intervention with treatments such as iron chelators to remove available iron or with hydroxyl radical scavengers such as dimethyl thiourea and dimethyl sulfoxide, virtually abolishes the onset of lung injury.[17]

It is also possible that a second sequence is involved in this reaction. H_2O_2 may be converted directly in an enzymatic fashion to halide dependent products, as shown in the following reaction:

$$H_2O_2 \xrightarrow[\text{halide and myeloperoxidase}]{} \underset{\text{chloramines and other products}}{\text{HOCl,}}$$

H_2O_2 is converted enzymatically by the neutrophil enzyme myeloperoxidase in the presence of halide to products such as hypochlorous acid (HOCl), stable chloramines, and other products. It has been suggested that products of this reaction are responsible for the ability of stimulated neutrophils *in vitro* to kill endothelial cells.[18] In experimental studies, protection by the interventions that deprive the system of iron or scavenge $HO^{\cdot}$ suggests that perhaps the bulk of the reaction sequence involves hydroxyl radical generation rather than myeloperoxidase products of H_2O_2.

The generation of the family of oxygen radicals is demonstrated in a simplified fashion by the following series of equations:

$$O_2 + e^{-} \rightarrow O_2^{-} \text{ (superoxide anion)}$$
$$O_2^{-} + e^{-} + H_2O_2$$
(hydrogen peroxide)
$$H_2O_2 + e^{-} \rightarrow O_2 + HO^{\cdot}$$
(hydroxyl radical) $+ OH^{-}$
$$HO^{\cdot} + e^{-} \rightarrow H_2O$$

This reaction sequence shows the sequential reduction of molecular oxygen through a four electron transfer process. Addition of the first electron results in O_2^{-}; the addition of a second electron generates H_2O_2. Addition of the third electron in the presence of iron, as described above in the Fenton reaction, produces $HO^{\cdot}$, and the final addition of the fourth electron results in the fully reduced form of oxygen, which is water.

Phagocytic cells, especially neu-

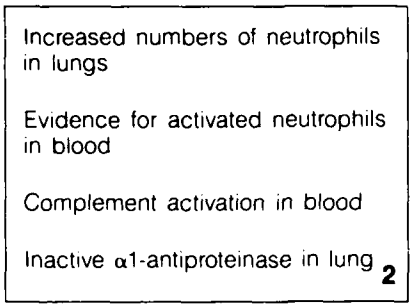


Fig. 2. *ARDS and evidence for linkage to neutrophils and complement activation.*

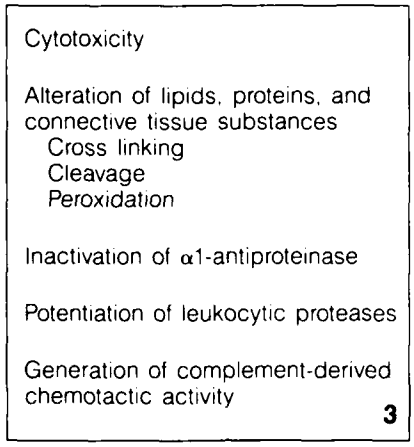


Fig. 3. *Consequences of oxygen radical formation.*

trophils, macrophages, and monocytes, are extraordinarily effective in producing this family of oxygen intermediates. Following stimulation of the cell membrane by chemotactic peptides or lipids, by activation of the Fc receptor, or by a combination of phagocytic stimuli and other agents, a membrane-associated enzyme, NADPH oxidase, is activated. NADPH is the enzyme responsible for initiating progressive reduction of molecular oxygen.[19-26] This system is associated with the main oxygen-dependent, bacteria-killing mechanism for ingested microbes.[27-34] If, however, the activated region of cell membrane is not rapidly internalized as a phagocytic vacuole, oxygen products will be generated on the surface of the cell and will diffuse toward potential targets.

It is now apparent that many types of acute inflammatory reactions, such as those induced by deposition of immune complexes, by complement activation, and by other means, bring about tissue injury because of the activation of phagocytic cells and their generation of oxygen radicals.[35-39] As indicated above, the acute lung injury seen in ARDS may follow a similar pathobiological mechanism.

The consequences of oxygen radical generation in tissues and in organs are multiple and varied (Figure 3). Cytotoxicity is the most well-known effect of oxygen radical formation. For instance, activation of neutrophils by phorbol myristate acetate can result in the destruction of red cells[35] and nucleated cells;[36-40] it has been clearly demonstrated that the cytotoxicity is due to oxygen radical generation.

There is chemical evidence that oxygen radical formation in tissues is associated with chemical changes in lipids, proteins, and connective tissue substances such as collagens and glycosaminoglycans.[41-46] It appears that most of these changes are probably caused by the oxidant effects of the oxygen radicals. Cross-linking of proteins has been described, and cleavage of lipids and peroxidation of lipids and other moieties all have been associated either in vitro or in vivo with oxgen radical formation.[42,43,47]

Another manifestation of chemical change associated with oxygen radical formation is that the chief antiprotease of the body, α1-antiproteinase, undergoes a relatively reversible activity change due to the oxidative conversion of a methionyl residue to a sulfoxide.[42] Inactive α1-antiproteinase has been described in the bronchoalveolar lavage fluids of patients with ARDS,[14] as well as in bronchoalveolar lavage fluids of animals injected intratracheally with formyl peptides.[49]

Recently it has been demonstrated that oxygen radicals can potentiate the activities of leukocytic proteases by an alteration of the substrate that is not associated with substrate hydrolysis itself.[50] This implies that when oxygen radicals have been formed, leukocytic proteases not only are fully active because of the loss of α1-antiproteinase, but also are actually potentiated because of subtle conformational changes in their substrates.

Finally, there is now preliminary evidence that oxygen radicals have the ability to generate chemotactic activity in serum that appears to be related to the fifth component of the complement.[51] The mechanism by which oxygen radicals bring about activation of the complement system has yet to be determined.

Conclusion

It seems clear that oxygen radicals play an important biological role in ARDS and in the other experimental models cited. Oxygen radicals also may be important to other biological reactions. It has been demonstrated that immune-complex-induced lung injury and glomerulonephritis are associated with oxygen radical production, and that interruption of this process will protect the tissue from injury.[52,53]

There is also evidence that ischemia and ischemic reperfusion injury of the heart and of the small bowel are associated with oxygen radical production. This may be caused by activated phagocytic cells or by tissue-associated enzymes. Xanthine dehydrogenase is converted during ischemia to xanthine oxidase, which then has the potential to generate O_2^- in tissues.[54-56] Even the diffuse vascular injury associated with experimental malaria[57] and the progressive neurological symptoms associated with allergic encephalomyelitis[58] have been found to be associated with oxygen radical production. Interventions that interfere with hydroxyl radical formation are markedly protective in these experimental disease states.

Thus there is accumulating evidence that oxygen radicals are important in a wide variety of diseases. Continued study of their mechanisms of formation and biological effects will yield important clues for intervention in ARDS and in other human illnesses.

References

1. Asbaugh DG, Bigelow DB, Petty TL: Acute respiratory distress in adults. *Lancet* 1967;2:319-323.

2. Petty TL, Asbaugh DG: The adult respiratory distress syndrome [clinical features, factors influencing prognosis and principles of management]. *Chest* 1971, 60:233-244.

3. Lamy M, Fallat RJ, Koenigen E, et al: Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. *Am Rev Respir Dis* 1975;114:267-283.

4. Sandritter WC, Mittermayer C, Riede UN, et al: Das Schocklungen-syndrom [ein allgemeiner Uberblick]. *Beitr Pathol*

1978;162:7-23.

5. Petty TL, Newman JH: Adult respiratory distress syndrome (medical progress). *West J Med* 1978;128:399-407.

6. Pietra GG, Ruttner JW, Wüst W, Glinz W: The lung after trauma and shock — Fine structure of the alveolar-capillary barrier in 23 autopsies. J Trauma 1981; 21:454-462.

7. Fowler AA, Hamman RF, Good JT, et al: Adult respiratory distress syndrome: Risk with common predispositions. *Ann Intern Med* 1983;98:593-597.

8. Bachofen M, Weibel ER: Structural alterations of lung parenchyma in the adult respiratory distress syndrome. *Clin Chest Med* 1982;3:35-56.

9. McGuire WW, Spragg RG, Cohen HB, et al: Studies on the pathogenesis of the adult respiratory distress syndrome. *J Clin Invest* 1982;69:543-553.

10. Zimmerman GA, Renzetti AD, Hill HR: Functional and metabolic activity of granulocytes from patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1983;127:290-300.

11. Hällgren R, Borg T, Venge P, et al: Signs of neutrophil and eosinophil activation in adult respiratory distress syndrome. *Crit Care Med* 1984;12:14-18.

12. Duchateau J, Haas M, Schreyen H, et al: Complement activation in patients at risk of developing the adult respiratory distress syndrome. *Am Rev Respir Dis* 1984;130:1058-1064.

13. Hammerschmidt DE, Weaver LJ, Hudson LD, et al: Association of complement activation and elevated plasma-C5a with adult respiratory distress syndrome. *Lancet* 1980;1:947-949.

14. Cochrane CG, Spragg R, Revak SD: Pathogenesis of the adult respiratory distress syndrome. Evidence of oxidant activity in bronchoalveolar lavage fluid. *J Clin Invest* 1983;71:754-761.

15. Carp H, Janoff A: In vitro suppression of serum elastase-inhibitory capacity by reactive oxygen species generated by phagocytosing polymorphonuclear leukocytes. *J Clin Invest* 1979;63:793-797.

16. Till GO, Johnson KJ, Kunkel R, et al: Intravascular activation of complement and acute lung injury. Dependency on neutrophils and toxic oxygen metabolites. *J Clin Invest* 1982;69:1126-1135.

17. Ward PA, Till GO, Kunkel R, et al: Evidence for role of hydroxyl radical in complement and neutrophil dependent tissue injury. *J Clin Invest* 1983;72:789-801.

18. Weiss SJ, Young J, LoBuglio AF, et al: Role of hydrogen peroxide in neutrophil-mediated destruction of cultured endothelial cells. *J Clin Invest* 1981;68: 714-721.

19. Drath DB, Karnovsky ML: Superoxide production by phagocytic leukocytes. *J Exp Med* 1975;141:257-261.

20. Becker EL, Sigman M, Oliver JM: Superoxide production induced in rabbit polymorphonuclear leukocytes by synthetic chemotactic peptides and A23187: The nature of the receptor and the requirements for Ca^{2+}. *Am J Pathol* 1979; 95:81-98.

21. Klebanoff SJ: Oxygen metabolism and the toxic properties of phagocytosis. *Ann Intern Med* 1980;93:480-489.

22. Root RK, Metcalf J, Oshino N, et al: H_2O_2 release from human granulocytes during phagocytosis: I. Documentation, quantitation, and some regulating factors. *J Clin Invest* 1975;55:945-955.

23. Goldstein IM, Roos D, Kaplan HB, et al: Complement and immunoglobulins stimulate superoxide production by human leukocytes independently of phagocytosis. *J Clin Invest* 1975;56: 1155-1163.

24. Simchowitz L, Mehta J, Spilberg I: Chemotactic factor-induced generation of superoxide radicals by human neutrophils: Effect of metabolic inhibitors and anti-inflammatory drugs. *Arthritis Rheum* 1979;22:755-762.

25. Patriarca P, Cramer R, Moncalvo S, et al: Enzymatic basis of metabolic stimulation in leukocytes during phagocytosis: The role of activated NADPH oxidase. *Arch Biochem Biophys* 1971;145:255-262.

26. McPhail LC, DeChatelet LR, Shirley PS: Further characterization of NADPH oxidase activity of human polymorphonuclear leukocytes. *J Clin Invest* 1976; 58:774-780.

27. Sbarra AJ, Karnovsky ML: The biochemical basis of phagocytosis: I. Metabolic changes during the ingestion of particles by polymorphonuclear leukocytes. *J Biol Chem* 1959;234:1355-1362.

28. DeChatelet LR: Oxidative bactericidal mechanisms of polymorphonuclear leukocytes. *J Infect Dis* 1975;131:295-303.

29. Babior BM: Oxygen-dependent microbial killing by phagocytes. *N Engl J Med* 1978;298:659-668, 721-725.

30. Babior BR, Kipnes R, Curnutte J: Biological defense mechanisms. The production by leukocytes of superoxide, a potential bactericidal agent. *J Clin Invest* 1973;52:741-744.

31. Klebanoff SJ: Iodination of bacteria: A bactericidal mechanism. *J Exp Med* 1967;126:1063-1078.

32. Klebanoff SJ: A peroxidase mediated antimicrobial system in leukocytes. *J Clin Invest* 1967;46:1078-1085.

33. McRipley RJ, Sbarra AJ: Role of the phagocyte in host parasite interactions: XII. Hydrogen peroxide-myeloperoxidase bactericidal system in the phagocyte. *J Bacteriol* 1967;94:1425-1430.

34. Klebanoff SJ: Myeloperoxidase-halide-hydrogen peroxide antibacterial system. *J Bacteriol* 1968;95:2131-2138.

35. Klebanoff SJ, Clark RA: Hemolysis and iodination of erythrocyte components by a myeloperoxidase-mediated system. *Blood* 1975;45:699-707.

36. Simon RH, Scoggin CH, Patterson D: Hydrogen peroxide causes fatal injury to fibroblasts exposed to oxygen radicals. *J Biol Chem* 1981;256:7181-7186.

37. Clark RA, Klebanoff SJ, Einstein AB, et al: Peroxidase-H_2O_2-halide system: Cytotoxic effect on mammalian tumor cells. *Blood* 1975;45:161-170.

38. Clark RA, Klebanoff SJ: Myeloperoxidase-mediated platelet release reaction. *J Clin Invest* 1979;63:177-183.

39. Sacks T, Moldow CF, Craddock PR, et al: Oxygen radical mediated endothelial cell damage by complement-stimulated granulocytes. An in vitro model of immune vascular damage. *J Clin Invest* 1978;61:1161-1167.

40. Martin WJ: Neutrophils kill pulmonary endothelial cells by a hydrogen-peroxide-dependent pathway. An in vitro model of neutrophil-mediated lung injury. *Am Rev Respir Dis* 1984;130:209-213.

41. Clark RA, Klebanoff SJ: Chemotactic factor inactivation by the myeloperoxidase-hydrogen peroxide-halide system. An inflammatory control mechanism. *J Clin Invest* 1979;64:913-920.

42. Petrone WF, English DK, Wong K, et al: Free radicals and inflammation: The superoxide dependent activation of a neutrophil chemotactic factor in plasma. *Proc Nat Acad Sci [USA]* 1980;77:1159-1163.

43. Perez HD, Weksler BB, Goldstein IA: Generation of a chemotactic lipid from arachidonic acid by exposure to a superoxide-generating system. *Inflammation* 1980;4:313-328.

44. McCord JM: Free radicals and inflammation: Protection of synovial fluid by superoxide dismutase. *Science* 1974; 185:529-551.

45. Parellada P, Planas JM: Synovial fluid degradation induced by free radicals: In vitro action of several free radical scavengers and anti-inflammatory drugs. *Biochem Pharm* 1978;27:535-537.

46. Greenwald RA, Moy WW: Effect of oxygen-derived free radicals on hyaluronic acid. *Arthritis Rheum* 1980;23: 455-463.

47. Barber AA, Bernheim F: Lipid peroxidation: Its measurement, occurrence, and significance in animal tissues. *Adv Gerontol Res* 1967;2:355-401.

48. Carp H, Janoff A: Possible mechanisms of emphysema in smokers. In vitro suppression of serum elastase-inhibitor capacity by fresh cigarette smoke and its prevention by antioxidants. *Am Rev Respir Dis* 1978;118:617-621.

49. Schraufstätter JU, Revak SD, Cochrane CG: Proteases and oxidants in experimental pulmonary inflammatory injury. *J Clin Invest* 1984;73:1175-1184.

50. Fligiel SEG, Lee EC, McCoy JP, et al: Protein degradation following treatment with hydrogen peroxide. *Am J Pathol* 1984;115:418-425.

51. Shingu M, Nobunaga M: Chemotactic activity generated by human serum from the fifth component of complement by hydrogen peroxide. *Am J Pathol* 1984; 117:201-206.

52. Johnson KJ, Ward PA: Role of oxygen metabolites in immune complex injury of lung. *J Immunol* 1981;126:2365-2369.

53. Rehan A, Johnson KJ, Wiggins RC, et al: Evidence for the role of oxygen radicals in acute nephrotoxic nephritis. *Lab Invest* 1984;51:396-403.

54. Granger DN, Rutili G, McCord JM: Superoxide radicals in feline intestinal ischemia. *Gastroenterology* 1981;81: 22-29.

55. Parks DA, Bulkley GB, Granger DN: Role of oxygen-derived free radicals in digestive tract diseases. *Surgery* 1983; 94:415-422.

56. Chambers DE, Parks DA, Patterson G, et al: Xanthine oxidase as a source of free radical damage in myocardial ischemia. *J Mol Cell Cardiol.* 1985, in press.

57. Clark IA, Hunt NH: Evidence of reactive oxygen intermediates causing hemolysis and parasite death in malaria. *Infect Immun* 1983;39:1-6.

58. Bowern NE, Ramshaw IA, Clark IA, et al: Inhibition of autoimmune neuropathological process by treatment with an iron-chelating agent. *J Exp Med* 1984; 160:1532-1543.

SPECIAL CONTRIBUTION
opioids, shock, thyrotropin releasing hormone

Naloxone and TRH in the Treatment of Shock and Trauma: What Future Roles?

Endogenous opioid peptides are released in response to stressful situations, such as circulatory shock, both as hormones and as central and peripheral neurotransmitters. Naloxone, an opiate antagonist, improves cardiovascular function in a variety of animal models of shock caused by endotoxemia, hemorrhage, anaphylaxis, or spinal trauma. Administration of thyrotropin-releasing hormone (TRH) in supraphysiologic doses also has pressor effects in these shock models. Given acutely after injury, TRH improves recovery in models of spinal trauma; however, the experimental effects of TRH do not involve action at the opiate receptor. Clinical evaluation of the use of naloxone in patients with shock has been largely limited to treatment of sepsis. The paucity of prospective, randomized trials makes these clinical data difficult to evaluate, but in septic patients the use of naloxone does not seem to improve survival. The use of naloxone in shock of other etiologies has not been clinically investigated, and may hold greater promise. Acute phase treatment of spinal trauma victims with TRH is currently undergoing clinical trials. [Bernton EW: Naloxone and TRH in the treatment of shock and trauma: What future roles? Ann Emerg Med August 1985;14:729-735.]

Edward W. Bernton, MD
Washington, DC

From the Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, DC

Presented at the 1985 UAEM/BIEM Research Symposium in Orlando, Florida, February 7-8, 1985.

Address for reprints: Edward W. Bernton, MD, Department of Medical Neurosciences, Walter Reed Army Institute of Research, WRAMC, Washington, DC 20307-5100.

Introduction

The physiological role of the endogenous opiate peptides has been the subject of intense research and continuing speculation since they were discovered ten years ago. They are members of a family of small "regulatory" peptides, marked by distribution mainly in the gut and in both the central and peripheral nervous systems. These substances display a broad range of activities which challenge earlier ideas about the nature of neurotransmitters and endocrine function. A body of evidence implicates these opiate peptides, or opioids, as contributing to physiologic alterations seen in circulatory shock. This evidence is derived primarily from experiments using naloxone, a specific receptor antagonist of narcotics and of endogenous opioids. Naloxone has been shown to improve hemodynamics in a variety of animal models of hemorrhagic, septic, and neurogenic shock. Other regulatory peptides, such as thyrotropin-releasing hormone (TRH) and glucagon, improve hemodynamics in experimental shock models and may eventually be of therapeutic use in shock and trauma.

Biosynthesis, Localization & Release of Endogenous Opioids

A remarkable variety of opioid peptides have been identified in animal tissues and secretions. They are grouped in three families, each consisting of varied cleavage products of one of three unique precursor molecules (Table 1). First described were methionine enkephalin and leucine enkephalin, which contain five amino acids and differ only in their carboxy-terminus amino acid. Most opioid peptides share the "Tyr-Gly-Gly-Phe" sequence of the enkephalins at their amino terminus, but lack other sequence homology and vary markedly in length. The "enkephalin sequence" seems to be required for binding at the opiate receptor. Using these and other structure activity relationships, numerous pharmaceutically active opioid peptide analogues have been synthesized.

Beta endorphin (B-EP), a 31 amino acid peptide, was first isolated from the intermediate lobe of the pituitary gland. All endorphins are cleavage products

of the larger precursor pro-opiomelanocortin (POMC),[1] which contains the amino acid sequences of MSH, ACTH, and the endorphins. Release of ACTH from the pituitary is usually accompanied by release of endorphins, and both circulate in a hormonal fashion. Shortened and acetylated endorphin fragments are also found in the circulation and constitute part of what has been measured by radioimmunoassay as endorphin-like immunoreactivity in body tissues and fluids. POMC also has been found in the human adrenal cortex. B-EP is also found in brain neurons grouped in the arcuate nucleus and in restricted areas of hypothalamus as well as the nucleus tractus solitarius. These neurons have long axons projecting rostrally and caudally to distant brain structures. Although pituitary beta-endorphin is released in a hormonal fashion, the target tissues for this circulating opioid remain unknown. Recently lymphocytes have been reported to release ACTH and endorphins in response to stimulation with virus or endotoxin.[2] This may be another source of circulating opioids during sepsis.

The enkephalins are derived from their own larger precursor, pro-enkephalin A.[3] Large amounts of met- and leu-enkephalin, together with catecholamines, are found within the dense secretory granules of the adrenal medulla, which appears to be the main source of circulating enkephalin peptides. Stimulation of the splanchnic nerve releases enkephalins and catecholamines from the medulla into circulation. Enkephalins have a very short plasma half life due to rapid degradation by specific endopeptidases.[4] Enkephalins also are present in sympathetic ganglia and myenteric nerve plexi. Along with other neuropeptides, enkephalins appear to have cotransmitter functions at these autonomic synapses.[5,6] In contrast to endorphins in the central nervous system (CNS), enkephalins are found in rather diffusely distributed short interneurons in the periaqueductal and limbic areas of the brain, in the autonomic nuclei of the brain stem and hypothalamus, and in the dorsal horn of the spinal cord. Their localization in synaptic vesicles suggests a neurotransmitter function.

Dynorphin and its related peptides were discovered most recently and were first isolated from the posterior pituitary. Dynorphin appears to be processed at different sites from enkephalin and endorphin, from a unique precursor called proenkephalin B. Apparently dynorphin is secreted into the circulation from the posterior pituitary in a manner similar to that of vasopressin. In the CNS, dynorphin immunoreactivity is found in cell bodies and neurons in areas of the brain stem, spinal cord, anterior hypothalamus, and substantia nigra. Peripherally, dynorphin-containing nerve fibers have been identified in the prevertebral sympathetic ganglia and in the myenteric and submucosal enteric ganglia.

TABLE. *Opioid peptides and precursors*

Precursor	Active Peptide
Proopiomelanocortin (POMC)	Beta-endorphin (B-EP)
Pro-enkephalin A	Met-enkephalin Leu-enkephalin
Pro-enkephalin B	Dynorphin

In general, most cells do not release their stores of opiate peptides steadily. Instead, when homeostasis is disrupted by stress such as pain or hypotension, endogenous opioids are elaborated by their respective tissues. This is demonstrated by the remarkable absence of effect of the opioid antagonist naloxone on body temperature, cardiovascular parameters, feeding behavior, and so forth in nonstressed resting animals.[7] During circulatory shock, however, with or without sepsis, pain, or thermal stress, naloxone alters many of the physiologic and behavioral responses observed, implying that activation of endogenous opiate systems is contributing to those responses.

Historically pain and circulatory shock have been closely linked by clinicians. Shock accompanying surgery, traumatic injury, or febrile illness was recognized in the 18th and 19th centuries, and was thought to be the result of a perturbation of nervous system function. As late as 1896, the physician Eugene Boise wrote, "Shock is not severe hemorrhage, nor does hemorrhage imply shock." Shock is "profound irritation of the entire sympathetic nervous system . . . acting through a nerve center upon the heart." By 1890, a Cincinnati surgeon named George Crile began physiologic studies relating clinical shock to a fall in blood pressure. Eventually appreciation of the hemodynamic aspects of the shock state led to an appropriate therapy, volume expansion, which was well established by the end of World War I. Since then, the modern view of shock as a hypovolemic phenomenon has at times obscured the earlier appreciation that a CNS mechanism was intimately involved in the cardiovascular derangements of shock. The pressor effects of naloxone in circulatory shock[8] have been interpreted as evidence that endogenous opioids play a key role in CNS mechanisms contributing to circulatory dishomeostasis, thus redirecting attention to an older interpretation of the clinical picture we call shock.

Opiate Antagonists in Septic Shock

Intravenous administration of endotoxin (widely used as a model for septic shock) results in a rapid and precipitous fall in blood pressure in conscious rats. Based on the hypothesis that endogenous opioids activated by the stress of shock might act like large doses of morphine to depress circulatory function further, naloxone was tested using this model, and was found to reverse rapidly the acute hypotension that occurs with endotoxin.[9] Other experiments extended these findings. In rat endotoxic shock, the improvement in blood pressure following naloxone administration was found to be dose-related and stereospecific. The minimum effective dose was 0.1 mg/kg, and the stereo-isomer of naloxone, which does not bind at opiate receptors, was ineffective at equimolar doses.[10]

Reynolds and coworkers[11] administered naloxone (2 mg/kg bolus followed by 2 mg/kg/hr infusion) or saline to dogs made hypotensive by

infusion of *E coli*. Dogs given naloxone had improved arterial pressure, and this was found to be due to increased cardiac output and ventricular contractility. Peripheral vascular resistance was unaffected. Twenty-four-hour survival was significantly improved by naloxone treatment. Investigators working with live *E coli* sepsis in pigs, dogs, horses, and monkeys have demonstrated that naloxone treatment can attenuate granulocytopenia, acidosis, hemoconcentration, and hypotension.[5]

Circulating beta-endorphin levels are elevated during endotoxemia in monkeys and sheep, as well as in human patients suffering from sepsis.[8,9] Whether this is simply a marker of the endocrine pituitary response to stress (and causally unrelated to circulatory depression) remains open to question, as is whether the site of action of naloxone is central, peripheral, or both. Intracerebroventricular injection of naloxone partially reverses hypotension following intravenous endotoxin;[5] however, intracoronary artery injection of naloxone in amounts too small to be effective intravenously improves blood pressure and cardiac contractility following hemorrhagic shock in dogs.[10]

Recent evidence suggests that enkephalins can inhibit chronotropic and vascular contractile responses to catecholamines in vitro.[11,12] Naloxone could act peripherally in vivo to antagonize this effect. Naloxone also may have an action, not opiate-receptor-mediated, to inhibit superoxide production by activated neutrophils (personal communication, C Simpkins). Such neutrophils are thought to play a role in adult respiratory distress syndrome (ARDS) following shock. Both beta-endorphin and acetylated B-EP enhance neutrophil chemotaxis in vitro in physiologic concentrations.[13] Naloxone also has been found to prevent the increased pulmonary platelet trapping and platelet aggregation seen in endotoxin-shocked dogs.[14] Sequestration and degranulation of platelets and neutrophils in the lung is thought to be a causal factor of ARDS.

Opiate Antagonists in Hemorrhagic Shock

Acute hemorrhage produces profound neuroendocrine changes, including increased catecholamine and vasopressin release. This stress also could activate endogenous opiate systems. Naloxone improved blood pressure and cardiac output in dogs subjected to acute arterial hemorrhage.[15] Total peripheral resistance, heart rate, and portal venous pressure were unchanged. Additional studies with this model showed that increasing doses of naloxone produced progressive increases in cardiovascular performance as well as survival.[16] Recently naloxone treatment was shown to improve circulatory function and increase survival following severe hemorrhage in cynomolgus monkeys.[17]

Factors Affecting Response to Naloxone

Despite the experimental data presented above, the clinical indications for, and efficacy of, naloxone remain to be established. Animal studies have shown significant species variability in septic, hemorrhagic, and anaphylactic shock models in experiments utilizing a wide range of therapeutic agents, and this variability applies to naloxone as well. For example, Hinshaw found that naloxone increased blood pressure and survival following live *E coli* infusion in the dog, where sepsis causes a hypodynamic circulatory response.[18] In the baboon, which manifests first a hyperdynamic response to sepsis (as does man), early treatment with naloxone increases mortality.[18] Additional baboon studies now suggest that when naloxone is given later, during the hypodynamic phase, mortality seems to be decreased with naloxone (L Hinshaw, personal communication). Shock studies in animals often do not show correlation between acute improvements in arterial pressure and increased survival. Our incomplete knowledge of the physiologic role of endogenous opioids in shock limits our understanding of the mechanisms of naloxone's actions in shock.

It seems unlikely that the endogenous opioid systems have evolved without being an adaptive response contributing to survival. In the face of untreated hemorrhage, hypotension will reduce blood loss, sedation, hypothermia, and immobility reduce metabolic demands of hypoperfused tissues. Additionally, if peripheral effects of opioids include desensitization of adrenergic receptors, this could, in theory, decrease the down regulation of these receptors which occurs quite rapidly in the face of intense sympatho-medullary outflow during shock, and results in diminished responses to endogenous or exogenous catecholamines.[11,12] Nonetheless it might be advantageous during the course of resuscitation and definitive treatment to reverse such adaptive functions of endogenous opioids activated with shock. Well-controlled clinical trials and additional research into opioid mechanisms are needed.

Recognition that doses of naloxone that are effective in treating shock are two to three times greater than doses that maximally antagonize opiate analgesia led to investigation and characterization of the opiate receptor involved in shock. There are several subtypes of opiate receptors that mediate different effects and are distinguished by their avidity for binding different opioid ligands.[14] The "mu" receptor is primarily responsible for the analgesic effects of morphine. The "delta" receptor may be more involved in autonomic responses to opiates (ie, in shock). Naloxone preferentially antagonizes mu receptors more than delta receptors; therefore, higher doses of naloxone may be needed to overcome its lower affinity for delta receptors. The 0.4-mg mL dosage vial of naloxone available for reversal of opiate analgesia and respiratory depression represents less than 0.005 mg kg in an 80-kg human being. As noted above, considerably higher doses, usually between 1 and 5 mg kg, have been efficacious in most of the experimental animal studies. Use of many of the available 0.4 mg vials to attain high dosages in human beings is impractical, and introduces a possible risk of toxicity from the preservative in these vials.

An experimental delta receptor antagonist, M154,129, reverses endotoxic shock in rats at doses that have no significant effect on morphine analgesia.[14] In spinal trauma or ischemia, the opiate peptide dynorphin (which binds preferentially to the "kappa" opiate receptor) has been implicated as a possible contributor to neurologic pathophysiology.[17] Studies are in progress to evaluate therapy with specific kappa antagonists in spinal trauma and ischemia models. Because naloxone is only a weak antagonist at the kappa receptor, large doses are required to reverse hypotension and improve neurologic outcome in such models.

Blood pH alters the effects of opiate agonists and antagonists. Indeed

Gurll et al[17] have shown that in monkeys subjected to hemorrhagic shock, the greater the acidosis, the less the hemodynamic response to naloxone. Thus correction of systemic acidosis may be necessary to permit maximal response to naloxone. This is also the case with the catecholamines. The hemodynamic response to naloxone in endotoxic and hemorrhagic shock also has been shown to be blunted by cold ambient temperature.[17,19,20] The reasons for this effect are unknown.

Naloxone in Neurogenic Shock, Spinal Injury & Ischemia

Neurogenic shock, characterized by hypotension and other autonomic dysfunction following acute spinal cord transection, responds to treatment with naloxone. In anesthetized cats, rapid cord transection at C6-7 produced transient hypertension followed by protracted hypotension. This hypotension was rapidly and stereospecifically reversed by (-)naloxone given IV or intracerebroventricularly.[20] This suggests that hemodynamic responses to naloxone after spinal transection are mediated by opiate receptors within the CNS, perhaps involving vagal efferent pathways. Further studies examined naloxone treatment following spinal injury. Acute cervical cord injury was produced in anesthetized cats, resulting in severe spastic quadriparesis in control animals. In contrast, injection of naloxone as long as four hours following injury not only improved hemodynamic variables and spinal cord perfusion acutely, but also significantly reduced permanent neurologic impairment measured following a six-week recovery period.[21]

In rabbits, 20-minute occlusion of the infrarenal aorta produces an anterior spinal artery occlusion syndrome with development of permanent hindlimb paralysis in more than 90% of the animals. Pretreatment with naloxone (2 mg/kg) significantly reduces this neurologic deficit at 24 and 48 hours.[21] Unlike in studies of endotoxic shock, delta-selective opiate receptor antagonists are without effect on cord ischemia models, while the mu- and kappa-selective antagonist WIN 44,441 does decrease residual neurologic damage.

TRH in Spinal Injury & Anaphylactic Shock

Thyrotropin-releasing hormone (TRH), a tripeptide hypothalamic releasing factor, has potent physiologic and behavioral actions when given parenterally at pharmacologic doses.[21] These actions are independent of its endocrine effects on thyroid-stimulating hormone (TSH) release. Supraphysiologic doses of TRH result in arousal and in increased respiration, peristalsis, body temperature, pupil size, heart rate, and arterial pressure. Observations of these effects, all opposite those of opioids, prompted a trial of TRH as a physiologic antagonist of opioid effects. TRH was shown to reverse the cataleptic and hypothermic effects of beta-endorphin.[21] It was shown also that TRH does not antagonize the analgesic effects of beta-endorphin or morphine, and does not bind to the opioid receptor. As does naloxone, TRH improves blood pressure in spinal, septic, and hemorrhagic shock models.[5] Unlike naloxone, TRH has marked direct pressor and behavioral effects in normotensive, nonstressed animals and human beings.

The pressor response seems to be mainly the result of an increase in total peripheral resistance, rather than the result of improved cardiac function.[22] While the effects of naloxone in shock provide evidence for the contributory role of endogenous opioid systems in shock, the effects of TRH in shock merely demonstrate this peptide's known pharmacologic effects, without yielding similar insight into CNS mechanisms specific to shock. TRH does possess a practical advantage in the circumstances of traumatic injury: it does not act as naloxone does to reverse narcotic analgesia.

TRH has been investigated as a therapy following spinal cord injury. After blunt trauma to the exposed dura of the cervical cord in anesthetized cats, TRH improved blood flow to the cord, improved hypotension, lessened the severity and incidence of pulmonary edema, reduced mortality, and reduced the chronic neurologic deficit.[23] This last effect was seen with injection of TRH as long as 24 hours after spinal cord injury. In a four-way comparison using the cord trauma model described above, TRH was found to be more effective in improving neurologic outcome than was naloxone, which was in turn more effective than saline or high-dose dexamethasone.[24]

The mechanism of this TRH effect probably involves more than a transient improvement in arterial blood pressure. Intracellular calcium flux, oxygen radicals, and disturbed microcirculation all have been implicated in the progression of spinal injury, and could be affected by naloxone or TRH therapy. Six-fold elevation of plasma met-enkephalin levels has been reported in spinal shock patients; in the same group, treatment with 2 mg TRH decreased met-enkephalin levels to the normal range.[25] This suggests that TRH may alter the release or distribution of opioids following spinal injury. TRH has been given to human beings in doses of up to 500 mg (IV, during several hours) without dangerous side effects. Studies of the safety of TRH in acute spinal injury patients are near completion, and controlled clinical studies are scheduled to begin shortly.

Preliminary studies suggest also that TRH may be a useful therapy for anaphylactic shock. The hemodynamic effects of TRH seem well suited to correct the primary abnormality in this form of shock, ie, massive vasodilation. Moreover, anaphylactic shock, and the "anaphylactoid" shock induced experimentally with cobra venom, platelet-activating factor, or leukotriene D4, are often quite resistant to conventional therapy. In animal models, anaphylactic and anaphylactoid shock are reversed much more effectively by TRH than by naloxone.[26]

Reported Experience with Naloxone in Shock

Most of the published reports of naloxone treatment of shock are case reports that lack randomized controls. Most of these reports pertain to patients with septic shock whose oliguria, hypotension, and decreased mental status were unresponsive to steroids, volume expansion, and pressor catecholamines. Although some of the patients responded to varying doses of naloxone with rapid improvement in blood pressure, it is unclear whether the naloxone interventions led ultimately to any increase in survival. One randomized, controlled trial in 57 patients compared maximal standard therapy, including continuous dopamine and high-dose methylprednisolone, with the same therapy plus 0.01 mg/kg naloxone followed by 0.1 mg/kg naloxone.[27] Significant increases were noted in systolic blood

pressure and left ventricular stroke work index, as well as in circulating epinephrine and norepinephrine, following naloxone therapy. None of these changes was seen during the course of therapy in the control group. No increase in survival, however, was noted in the naloxone-treated group.

Peters and colleagues reported a series of 13 adult patients suffering sepsis who were treated with doses of naloxone ranging from 0.4 mg to 8 mg.[28] In nine patients without adrenocortical suppression, naloxone resulted in a mean increase of systolic BP from 79 ± 2 mm Hg to 109 ± 4 mm Hg. Only three of the nine patients ultimately survived, however. Four patients with probable adrenocortical insufficiency did not show a significant pressor response to naloxone.

Catherton et al reported that three newborns with Group B streptococcal sepsis were treated with 0.1 mg/kg naloxone following continued hypotension with conventional therapy. Systolic pressure increased by a mean of 21% ± 4%, and two of the infants survived.[29]

Groeger et al reported the cases of ten patients with refractory septic shock who were treated with 0.3 mg/kg naloxone. Five patients responded to naloxone; in those patients, systolic BP improved from a mean of 83 ± 4 mm Hg to 130 ± 16 mm Hg, and left ventricular stroke work index improved by more than 35%. No improvement in ultimate survival in the naloxone-responsive group was found.[30]

At doses ranging between 0.01 mg/kg and 0.2 mg/kg, naloxone was administered to 15 patients who had refractory hypotension following meningococcal sepsis.[31] Only three patients showed a sustained increase in mean arterial pressure of greater than 20 mm Hg following naloxone administration. Only four of the 15 patients survived. The adrenocortical function of these patients was not assessed, but it is a function that is often impaired following meningococcal septic shock. It has been hypothesized by Peters[28] that adrenocortical function is required for naloxone to improve hemodynamics in the shock state.

Bernard et al[32] administered naloxone within 24 hours following acute myocardial infarction in 20 patients. Eight patients in cardiogenic shock and unresponsive to IV dopamine showed an increase in systolic blood pressure greater than 20 mm Hg following 0.4 mg to 4 mg IV naloxone; three of these patients survived. Five patients with bradycardia and hypotension following inferior myocardial infarction were treated with 4 mg IV naloxone and they responded with improvement of heart rate and blood pressure. These authors did not state whether atropine was also used. Three of their five patients reported chest pain following naloxone. The authors did not state whether any new ischemic changes on ECG occurred at this time. Six patients with uncomplicated myocardial infarcts and normal heart rate and blood pressure received 4 mg naloxone with no change in these parameters and no subjective side effects.

In a recently published study, Rock and coworkers[33] reported that up to 3.1 mg/kg naloxone was administered to 12 septic patients who were unresponsive to volume replacement and vasopressors. Hypovolemia, acidosis, and hypoxemia were corrected before the protocol was begun; then hemodynamic baseline measurements were obtained. Only four patients responded to naloxone with increases in MAP. Statistical analysis revealed no significant change in any hemodynamic parameter following treatment with naloxone. Furthermore, four patients had adverse side effects following naloxone, including pulmonary edema, abrupt hypotension, and grand mal seizure.

Taken together, the clinical reports to date deal mainly with septic shock. Entry criteria for formal studies generally have included shock refractory to treatment with antibiotics, vasopressors, volume expansion and, in some cases, steroids. The clinical groups included in such septic shock studies display extensive and often prolonged hemodynamic compromise, multiple metabolic abnormalities, and (often) extensive underlying disease or multi-organ failure, or both. The frequent lack of response to naloxone in this population, in contrast to experimental animal studies, is not surprising. Animal studies use healthy animals made acutely hypotensive with endotoxin or bacteremia. The animals usually are not resuscitated with antibiotics, volume expansion, steroids, and vasopressors, with the nonresponders selected for naloxone therapy.

In the Hughes study, in which lack of response to conventional therapy was not an entry criterion, a hemodynamic response to naloxone appears to be demonstrated. Case reports of naloxone therapy show a pattern of beneficial response in patients who have no evidence of systemic disease or organ failure.*

Published reports — even anecdotal reports — of the use of naloxone in hemorrhagic or other hypovolemic shock are lacking. One reason is obvious: hypotension due to hypovolemia responds well to control of hemorrhage and aggressive volume replacement. Patients managed in this way are unlikely to meet the criterion of failure to respond hemodynamically. However, the clinical course can be complicated later by ARDS or acute renal failure, both of which may cause significant late morbidity. Animal studies of naloxone's effects in hypovolemic shock models may be more closely related to clinical efficacy than was the case with models of sepsis. Traumatic shock usually occurs in an otherwise healthy patient. This fact eliminates the variable of major preexisting illness which is present in septic patients but not in laboratory animals. A clinical trial of naloxone in traumatic and hypovolemic shock should involve its use to "buy time" for conventional therapy and then use as an adjunct to such therapy. Appropriate study parameters would include the incidence of death or major complications, such as ARDS and ARF, following resuscitation. One such study is now planned at a regional trauma center.

A subgroup of hypovolemic patients develop bradyarrhythmias or inappropriately low heart rates, and may be at high risk for imminent ventricular fibrillation or electromechanical dissociation (EMD).[34] Data from animal studies suggest that naloxone may prevent or reverse these changes, allowing time for control of bleeding and adequate volume expansion. Rothstein and coworkers have reported that of four dogs developing EMD following arrest, CPR, and electrical defibrillation, all developed a perfusing rhythm following 5 mg/kg naloxone.[35]

Obviously the importance of naloxone in clinical shock therapy will remain unknown unless large, well-controlled clinical trials are conducted. To date neither animal nor human studies offer clear guidance regarding the

clinical indications and efficacy of naloxone across the clinical spectrum of hemodynamic impairment encountered by the physician.

Dangerous side effects have occurred that are attributable to naloxone treatment of refractory septic shock, particularly in patients with severe systemic disease and organ failure. Sepsis itself can, of course, result in hyper- or hypoglycemia, but animal studies suggest that endogenous opiates can stimulate glucagon release and can mediate hyperglycemia following various stresses, including sepsis and hypovolemia. This effect is antagonized by naloxone.[36,37] Certainly septic patients receiving naloxone should be carefully monitored for the development of hypoglycemia until additional experience permits assessment of this risk.

Case reports to date give instances of dramatic hemodynamic response to naloxone. There are, however, many reports of no hemodynamic response or adverse effects. Even with good hemodynamic response, it is not established whether naloxone administration results in increased rates of survival. The factors responsible for, or that predict a clinical response to, naloxone have not been identified. Only prospective clinical studies with randomized controls will fill these gaps in our knowledge. The role of opiate antagonists in circulatory shock may remain an open question for some time.

Conclusions

Experiments with opioid antagonists reveal that endogenous opioid systems within the CNS are activated by stressful situations, such as shock. These systems are structurally localized to areas of the brain stem and midbrain, where they not only affect autonomic outflow, but also may integrate the limbic and emotional input to cardiovascular function. During shock, activation of endogenous opioid systems contributes to loss of circulatory homeostasis. In general, this may involve an inhibition of sympathetic outflow and, perhaps, augmentation of parasympathetic tone. Opioid antagonists reverse this effect.

Opioid peptides also are released peripherally following stresses, such as sepsis, from the pituitary, from the adrenal medulla, and (perhaps) from lymphocytes or macrophages. Opioid peptides have poorly understood peripheral actions. They are present in autonomic ganglia, and probably modulate synaptic traffic there; they act on the endocrine pancreas and affect insulin and glucagon release; they may regulate adrenergic receptor sensitivity to catecholamines; and they may affect neutrophil activation and chemotaxis. These peripheral effects of endogenous opioids must be better elucidated before the actions of opiate antagonists in shock states can be fully characterized. Currently the actions of naloxone in shock states appear to be mediated both centrally and peripherally. Research in this area has stimulated interest in examining the possible resuscitative uses of other neuropeptides, such as TRH and glucagon.

Clinical data on the safety and efficacy of TRH in treating spinal cord injury should be available soon. Currently the role of narcotic antagonists in the treatment of shock, although showing promise in experimental models, must be delineated by adequately controlled human trials.

References

1. Bernton EW, Long J, Holaday JW: Opioids and neuropeptides: Mechanisms in circulatory shock. *Fed Proc* 1985;44: 290-299.

2. Blalock EJ, Smith EM: A complete regulatory loop between immune and neuroendocrine systems. *Fed Proc* 1985;44: 108-111.

3. Prosdocimi M, Di Giulio AM, Finesso A, et al: Inhibitory role of opiates on ganglionic transmission, in Genazzani AR, Muller EE (eds): *Recent Progress in Opioid Research: Central and Peripheral Endorphins, Basic and Clinical Aspects.* New York, Raven Press, 1984, p 121.

4. Jan YN, Lily YJ: Coexistence and corelease of cholinergic and peptidergic transmitters in frog sympathetic ganglia. *Fed Proc* 1983;42:2929-2933.

5. Holaday JW: Cardiovascular effects of endogenous opiate systems. *Ann Rev Pharmacol Toxicol* 1983;23:541-594.

6. Holaday JW, Faden AI: Naloxone reversal of endotoxic hypotension suggests role of endorphins in shock. *Nature* 1978, 275:450-451.

7. Reynolds DG, Gurll NJ, Vargish T, et al: Blockade of opiate receptors with naloxone improves survival and cardiac performance in canine shock. *Circ Shock* 1980;7:39-48.

8. Gurll NJ, Reynolds DG, Vargish T, et al: Primate endotoxic shock reversed by opiate receptor blockade with naloxone. *Physiologist* 1981;24:118-123.

9. Weissglas IS: The role of endogenous opiates in shock: Experimental and clinical studies in vitro and in vivo, in Reichard S, Reynolds D, Adams H (eds): *Advances in Shock Research.* New York, Alan R Liss, 1983, vol 10, pp 87-94.

10. Lechner R, Gull N, Reynolds D: Intracoronary naloxone in hemorrhagic shock: Dose-dependent, stereospecific effects. *Am J Physiol* 1985, in press.

11. Eiden LE, Ruth JA: Enkephalins modulate the responsiveness of rat atria *in vitro* to norepinephrine. *Peptides* 1982; 3:475-478.

12. Ruth JA, Doerr AL, Eiden LE: Leuenkephalin inhibits norepinephrine-induced contraction of rat aorta. *Eur J Pharm* 1984;105:189-191.

13. Simpkins C, Dickey C, Fink M: Human neutrophil migration is enhanced by beta endorphin. *Life Sci* 1984;34: 2251-2255.

14. Almqvist P, Kuenzig M, Schwartz SI: Effect of naloxone on endotoxin-induced pulmonary platelet sequestration. *Acta Chir Scand* 1983;149:23-26.

15. Vargish T, Reynolds DG, Gurll NJ, et al: Naloxone reversal of hypovolemic shock in the dog. *Circ Shock* 1980,7: 31-38.

16. Gurll NJ, Reynolds DG, Vargish T, et al: Naloxone improves survival rate and cardiovascular function in canine hemorrhagic shock. *J Pharmacol Exp Ther* 1982, 220:625-628.

17. Gurll NJ, Reynolds DG, Vargish T, et al: Body temperature and acid-base balance determine cardiovascular responses to naloxone in primate hemorrhagic shock. *Fed Proc* 1982;41:1135-1138.

18. Hinshaw L, Beller B, Chang A, et al: Evaluation of naloxone for therapy of e coli shock: Species differences. *Arch Surg* 1985, in press.

19. Holaday JW, Faden AL: Naloxone acts at central opiate receptors to reverse hypotension, hypothermia, and hypoventilation in spinal shock. *Brain Res* 1980, 189:295-299.

20. Janssen H, Pugh JL, Lutherer LO: Reduced ambient temperature blocks the ability of naloxone to prevent endotoxin induced hypotension. *Adv Shock Res* 1982,7:117-124.

21. Faden AI: Opiate antagonists and thyrotropin releasing hormone: Potential role in the treatment of central nervous system injury. *JAMA* 1984;254:1452-1454.

22. Zaloga GP, Chernow B, Zaichuk R, et al: Diagnostic doses of protirelin (TRH) elevate BP by noncatecholamine mechanisms. *Arch Intern Med* 1984;144: 1149-1152.

23. Faden AI, Jacobs TP, Holaday JW:

Thyrotropin releasing hormone improves neurologic recovery after spinal trauma in cats. *N Engl J Med* 1981;305:1063-1067.

24. Faden AI, Jacobs TP, Smith MT, et al: Comparison of thyrotropin-releasing hormone (TRH), naloxone, and dexamethasone treatment in experimental spinal injury. *Neurology* 1983;33:673-678.

25. Survaprakash B, Goel AK, Pathak CM, et al: Thyrotropin releasing hormone decreases elevated plasma met-enkephalin levels in spinal cord injury, abstract. *Clin Res* 1984;32:246a.

26. Faden AI, Feuerstein G, Hayes E, et al: Leukotrienes and anaphylactic shock: A therapeutic role for thyrotropin-releasing hormone. *Circ Shock* 1983;10: 246-250.

27. Hughes GS: Naloxone and methylprednisolone enhance sympathomedullary discharge in patients with septic shock. *Life Sci* 1984;3:2319-2326.

28. Peters WP, Friedman PA, Johnson MW, et al: Naloxone in septic shock. *Lancet* 1981;1(8219):529-532.

29. Catherton A, Howick J, Oliver S: Naloxone in neonatal septic shock, abstract. *Clin Res* 1984;32:898a.

30. Groeger JS, Carlon GC, Howland WS: Naloxone in septic shock. *Crit Care Med* 1984;11:650-654.

31. Valdivielso A, Casado J, Ruiz A, et al: Naloxone and endotoxic shock. A wonder drug? *Ann Esp Pediatr* 1984;20:85-90.

32. Bernardi P, Grimaldi R, Adami C, et al: Effects of naloxone on cardiogenic shock in the course of acute myocardial infarction, in Meller E, Genazzani A (eds): *Central and Peripheral Endorphins: Basic and Clinical Aspects*. New York, Raven Press, 1984, pp 295-299.

33. Rock P, Silverman H, Plump D, et al: Efficacy and safety of naloxone in septic shock. *Crit Care Med* 1985;13:28-33.

34. Secher NH, Jensen KS, Warner C, et al: Bradycardia during severe but reversible hypovolemic shock in man. *Circ Shock* 1984;14:267-274.

35. Rothstein RJ, Niemann JT, Rennie CJ, et al: Use of naloxone during cardiac arrest and CPR: A potential adjunct for post-countershock electromechanical dissociation, abstract. *Ann Emerg Med* 1984;13:394.

36. Ipp E: Central and peripheral endorphins: The role in the control of glucose homeostasis, in Muller E, Genazzani A (eds): *Central and Peripheral Endorphins: Basic and Clinical Aspects*. New York, Raven Press, 1984, pp 251-257.

37. Bereiter DA, Plotsky PM, Gann DS: Selective opiate modulation of the physiological responses to hemorrhage in the cat. *Endocrinology* 1983;113:1439-1446.

To prevent exercise-induced bron[illegible]spasm

VENTOLIN®
(ALBUTEROL/GLAXO)
INHALER AND REFILL

With its highly effective therapeutic action that goes to work with[illegible]es...with its unsurpassed β_2 selectivity*...VE[illegible]inhaler is clearly an agent of choice[1] for[illegible]venting exercise-induced bronchospasm in yo[illegible]ctive, asthmatic patients.

- Inhaled route [illegible]livery of medication directly [illegible]
- Minim[illegible]commended dosest
- Accepted b[illegible]onal Olympic Committee (IOC)[illegible]by athletes in international competition

*Bronchoselectivity denotes a relative preference for β_2 adrenergic receptors located chiefly in the bronchial tissues. This preference is not absolute.
†Sympathomimetic amines should be used with caution in patients with cardiovascular disorders. See Prescribing Information.
1. Sly RM: Beta-adrenergic drugs in the management of asthma in athletes. *J Allergy Clin Immunol* 1984;73(part 2):680-685.

[illegible]leader in respiratory care

Glaxo Inc.[illegible]NC 27709

[illegible]

[illegible] is indicated for the relief of bronchospasm in patients with reversible obstructive [illegible]disease, and for the prevention of exercise-induced bronchospasm.

CONTRAINDICATIONS: VENTOLIN® Inhaler is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS: As with other adrenergic aerosols, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

The contents of VENTOLIN® Inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

PRECAUTIONS: Although it has less effect on the cardiovascular system than isoproterenol at recommended dosages, albuterol is a sympathomimetic amine and as such should be used with caution in patients with cardiovascular disorders including coronary insufficiency and hypertension, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes and ketoacidosis. The relevance of this observation to the use of VENTOLIN® Inhaler is unknown, since the aerosol dose is much lower than the dose given intravenously.

Although there have been no reports concerning the use of VENTOLIN Inhaler during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information for Patients: The action of VENTOLIN® Inhaler may last up to six hours and therefore it should not be used more frequently than recommended. Do not increase the number of frequency of doses without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking VENTOLIN Inhaler, other inhaled medicines should not be used unless prescribed. See *Illustrated Patient's Instructions* For Use.

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a 2 year study in the rat, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomata of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalational dose. The relevance of these findings to humans is not known. An 18-month study in mice revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects: *Pregnancy Category C:* Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg, corresponding to 14, 14, and 140 times the maximum human inhalational dose) showed a cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 or 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 2,800 times the maximum human inhalational dose.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS: Side effects to albuterol are similar to other sympathomimetic agents. Those most frequently observed are palpitations, tachycardia, and increased blood pressure; tremor, nausea, dizziness, heartburn, and nervousness.

Albuterol can also cause hypertension, angina, vomiting, vertigo, central stimulation, insomnia, headache, unusual taste, and drying or irritation of the oropharynx. Overdosage can exaggerate these side effects.

HOW SUPPLIED: VENTOLIN® Inhaler, 17.0 g canister, box of one. It is supplied with an oral adapter and patient's instructions (NDC 0173-0321-88). Also available: VENTOLIN® Inhaler Refill, 17.0 g canister only with patient's instructions (NDC 0173-0321-98). Each metered-dose canister provides at least 200 oral inhalations of 90 mcg per inhalation.

For full prescribing information, please consult Package Insert.

Succeed in Managing YOUR Practice Through . . .

MANAGEMENT STRATEGIES IN EMERGENCY MEDICINE

A New Workshop Presented By

THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS

This intensive workshop will enable you to:

- Select malpractice coverage designed to meet your needs
- Develop short and long-range plans to direct your practice growth
- Optimize third-party reimbursement
- Recognize opportunities available through joint ventures with other health care providers
- Effectively contain costs without sacrificing quality
- Reduce medicolegal risks within your facility
- Create realistic staffing guidelines
- Establish and implement effective policies and procedures
- Determine your markets and increase your market share
- Prepare and negotiate comprehensive contracts
- Identify opportunities for computer applications in your practice
- Initiate successful billing techniques
- Apply strategies to help you work more effectively within the Medicare system
- Develop an innovative PR plan
- Establish positive patient relations

No matter what your practice setting, hospital emergency department or ambulatory care center, this is the program for YOU!

- Emergency physicians
- Group directors
- Operations managers
- Billing personnel

This program has been approved for 25 hours of ACEP Category I credit

NOVEMBER 18-20, 1985

Hyatt Regency New Orleans
New Orleans, Louisiana

ACEP Members — $440.00*
Physician Non-members — $490.00*
Administrator/Others — $490.00*

*Includes a comprehensive resource manual providing in-depth coverage of all topics, opening reception and all coffee breaks

Hyatt Regency New Orleans
$76.00 Single or Double

For a complete program brochure call or write:

ACEP, P.O. Box 619911, Dallas, Texas 75261-9911, 214/659-0911

SPECIAL CONTRIBUTION
brain ischemia, brain ultrastructure,
calcium, calcium antagonists

Ischemic Brain Injury and Cell Calcium: Morphologic and Therapeutic Aspects

Histopathological data obtained from different experimental models of hypoxia and ischemia were evaluated in order to extend current knowledge of mechanisms responsible for delayed neuronal cell death. Special attention is given to the distribution of calcium (Ca^{2+}) in vulnerable areas during the postischemic period. Between an initial defensive Ca^{2+} sequestration, which is completely reversible, and final toxic Ca^{2+} overload, which is associated with irreversible neuronal necrosis, important Ca^{2+} shifts could be demonstrated cytochemically. Such shifts occur mainly at excitatory presynaptic sites and seem to precede structural ischemic cell change in postsynaptic areas. Recent results obtained with some Ca^{2+} entry blockers indicate that prophylactic treatment and postischemic intervention prevent cytosolic Ca^{2+} overload and reduce delayed brain injury. [Van Reempts J, Borgers M: Ischemic brain injury and cell calcium: Morphologic and therapeutic aspects. Ann Emerg Med August 1985;14:736-742.]

Jos Van Reempts
Marcel Borgers, DrSc
Beerse, Belgium

From the Department of Life Sciences, Janssen Pharmaceutica, Beerse, Belgium

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985

Address for reprints: Jos Van Reempts, Laboratory of Neurocytology, Department of Life Sciences, Janssen Pharmaceutica, B-2340 Beerse, Belgium

Introduction

Irreversible structural disintegration of the neuron is the final stage of a series of complicated pathophysiological processes that may follow an ischemic or hypoxic brain insult. Evaluation of morphologic changes is therefore important, not only to study the mechanisms that underlie such injury, but also to study the effects of antianoxic pharmacological treatment.

In the past five years, interesting reviews have appeared in which the complicated pathology of ischemic brain injury is discussed in detail.[1-3] Among the hypotheses put forward, the concept of toxic Ca^{2+} overload remains very attractive because several other biochemical events related to ischemia may result directly from abnormal increase of intracellular Ca^{2+} concentration.[3,4] Ca^{2+} is involved in normal cell function, particularly in active processes such as neurotransmission; however, altered membrane permeability for this cation (as a result of hypoxia, for example) may have dramatic consequences for the cell.[5] Using cytochemical techniques, we have shown that irreversible neuronal damage is associated with considerable intracellular Ca^{2+} overload.[6] With cytochemical techniques it was not possible to demonstrate a causal relationship between Ca^{2+} overload and cell death, but several other studies suggest the pivotal role of increased Ca^{2+} accumulation in processes leading to irreversible neuronal destruction.[1,5]

The reasons why some areas in the brain are more vulnerable than others to Ca^{2+} overload are not well understood. Although vascular determinants may be important, metabolic aspects merit a greater consideration.[7] Synaptic release of excitatory transmitters (glutamate, aspartate) is now thought to be important in selective neuronal necrosis.[7-9] Moreover, there are numerous indications that receptor sensitivity to glutamate-induced depolarization at the postsynaptic membrane is triggered by Ca^{2+}.[10,11] As a consequence, one can hypothesize that damage to the brain should be reduced when Ca^{2+}-triggered transmitter release or postsynaptic Ca^{2+} accumulation, or both, are suppressed by Ca^{2+} entry blockers.

We review the histopathological picture in different experimental models of brain areas at risk. Special attention is given to changes in distribution of subcellular Ca^{2+}. Some new data on the protective effect of Ca^{2+} entry blockers also are included.

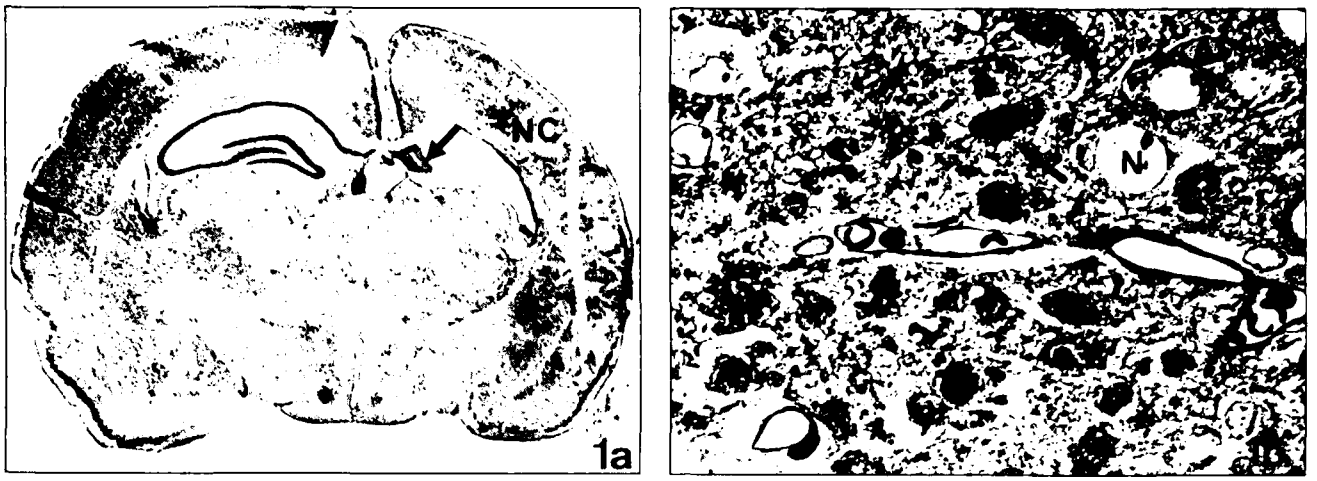


Fig. 1: *Light microscopic appearance of the brain of a 3-week-old rat with unilateral carotid artery ligation and exposed to 8% oxygen for 2 hr at an age of 7 days. A whole-mount coronal section (A, x 6) shows severe atrophy of the ipsilateral hippocampus (arrow) and neocortex (NC); the contralateral hemisphere remains unaffected. At higher magnification (B, x 750), a characteristic morphologic picture is found, resembling that of the adult hypoxic rat. Ischemic cells undergo coagulative cell change (black arrow) or edematous cell change (white arrow), and can be easily discerned from normal neurons (N) and astrocytes (A).*

Histopathological Data from Current Experimental Models

The neuropathological aspect and the functional severity of cerebral damage are dependent on the type of applied insult. It is a well-recognized phenomenon that incomplete ischemia is worse than complete ischemia.[1] Moreover, the vulnerability of certain brain areas may differ in relation to hypoxic and ischemic insults.[12] The experimental models that have been used include both hypoxia and ischemia. All permitted prolonged survival of the animals. Early postinsult phenomena as well as delayed neuronal cell death thus could be studied.

In the hypoxia study, oxygen supply was reduced in adult rats by intermittent exposure to pure nitrogen[13] and in neonatal rats by prolonged exposure to 8% O_2.[14] In both groups, one hemisphere was made selectively vulnerable by a preceding, unilateral carotid artery occlusion. In the ischemia study, incomplete ischemia was obtained either by transient occlusion of both carotid and vertebral arteries (four-vessel occlusion, 4-VO)[15] or by a combination of bilateral carotid artery clamping and severe hypotension (two-vessel occlusion, 2-VO).[16]

The most striking neuropathological outcome was found after prolonged hypoxia in the neonatal rats. Two weeks after seven-day-old rats underwent a two-hour exposure to 8% O_2, a severe atrophy of one cerebral hemisphere was visible (Figure 1A). The degree of damage was related directly to the duration of hypoxia, and it is correlated with a release of vasoactive amines during the hypoxic insult.[14] Cell changes in vulnerable areas were similar to those observed in the adult hypoxic and ischemic rats and could be classified as coagulative necrosis of neurons and edematous cell change of astrocytes (Figure 1B). Moreover, in incomplete ischemia models, delayed damage was most pronounced and strictly limited to the CA_1 region of the hippocampus (Figure 2).[15-17] In contrast, changes during early recirculation periods consisted of microvacuolation localized over the entire hippocampus. This change is considered to represent reversible cell changes.[15]

Subcellular Morphology and Ca^{2+} Distribution

A more detailed description of ultrastructural cell changes and subcellular Ca^{2+} distribution at different intervals after an ischemic episode may help us obtain better insight into structural and cytochemical phenomena that cause a neuron to become irreversibly damaged. Once central nervous system (CNS) tissue is below threshold values of cerebral blood flow (CBF) and arterial O_2 tension, Ca^{2+} translocates from the extracellular to the intracellular space.[11] Ca^{2+} can be visualized in the electron microscope as electron-dense precipitates. In the normal brain, such precipitates are very scarce. Only synaptic vesicles and (to a lesser extent) mitochondria contain single precipitates.

In previous reports, we found that in far-advanced stages of cell damage, the intracellular Ca^{2+} content is augmented dramatically.[9,12,15] Accumulations of Ca^{2+} precipitate were encountered in swollen mitochondria, in swollen cell processes, in nuclei, and in cytoplasmic vacuoles of coagulated neurons. Ca^{2+} movements during the early phase of reperfusion after a 20-minute period of 4-VO[15] deserve special attention. Large amounts of precipitate were found in swollen mitochondria, swollen cell processes, and nuclei; however, they also occurred in similar amounts in areas that recovered and survived. It was therefore concluded that such Ca^{2+} loading, which was concomitant with microvacuolation and edematous swelling, could reflect an in-built defense mechanism. After restoration of cerebral circulation, all cells regained their normal structure.

This neuronal recovery was of short duration, however, in vulnerable areas. Neuronal destruction became apparent after 24 hours. Our observations led us to conclude that increased intracellular Ca^{2+} did not necessarily

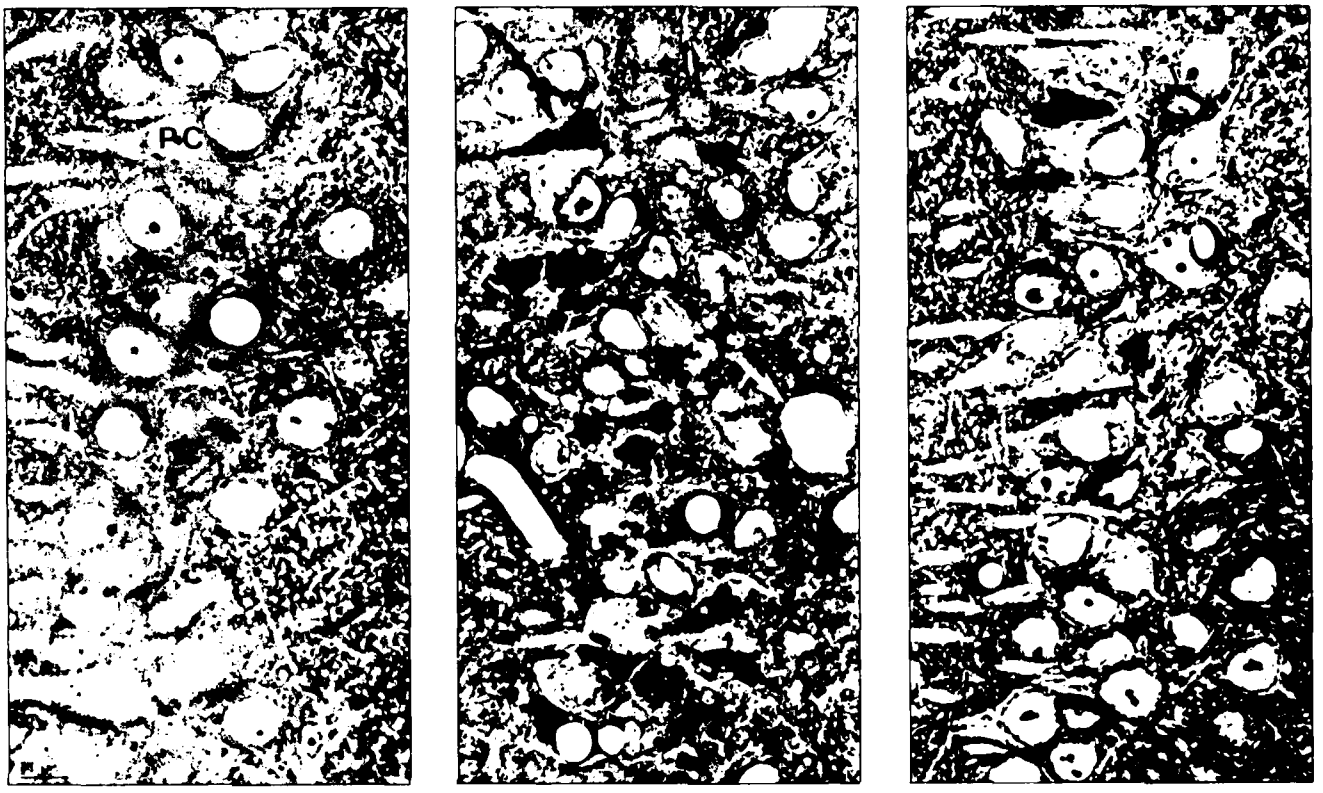


Fig. 2. *Detail of the hippocampal CA_1 pyramidal cell layer of a normal rat (A, × 700), of an untreated, ischemic rat (B, × 700), and of a flunarizine-treated ischemic rat (C, × 700) who survived three days after a 20 minute 4 VO episode. In the normal rat (A), pyramidal cells (PC) and astrocytes (A) appear well preserved. Ischemic areas (B) are characterized by coagulative cell change of neurons (black arrow) and edematous cell change of astrocytes (white arrow). Damage has been drastically reduced (C) when flunarizine was given IP at a dose of 0.1 mg/kg two minutes before recirculation, and PO at two daily doses of 10 mg/kg during the recirculation period.*

mean that cells were irreversibly damaged. Similar observations were reported by Griffiths et al,[18] who studied microvacuolation and Ca^{++} influx in rats after recovery from L-allylglycine-induced seizures. Thus it is clear that in vulnerable areas such as the CA_1 pyramidal cell layer of the hippocampus, other phenomena in addition to the initial Ca^{++} influx are determinant for the induction of irreversible neuronal degeneration.

In the 2 VO model of Smith et al,[19] CBF could be reliably reduced to values below 5 mL/100 g/min. To obtain an acceptable survival rate, the ischemic period was limited to 8 minutes. In this way, it was possible to follow Ca^{++} shifts by time intervals. Events in the hippocampal CA_1 layer occurred as follows:

1) During ischemia, a pronounced intracellular edema is formed, which in the light microscope appears as microvacuolation. Mitochondria, astrocytes, and dendrites appear swollen and contain huge amounts of Ca^{++} precipitate (Figure 3A).

2) Microvacuolation and the concomitant Ca^{++} accumulation disappear in all regions within 15 minutes postischemia, indicating that cytosolic Ca^{++} surplus may still be removed from the cell body once oxygen supply is restored.

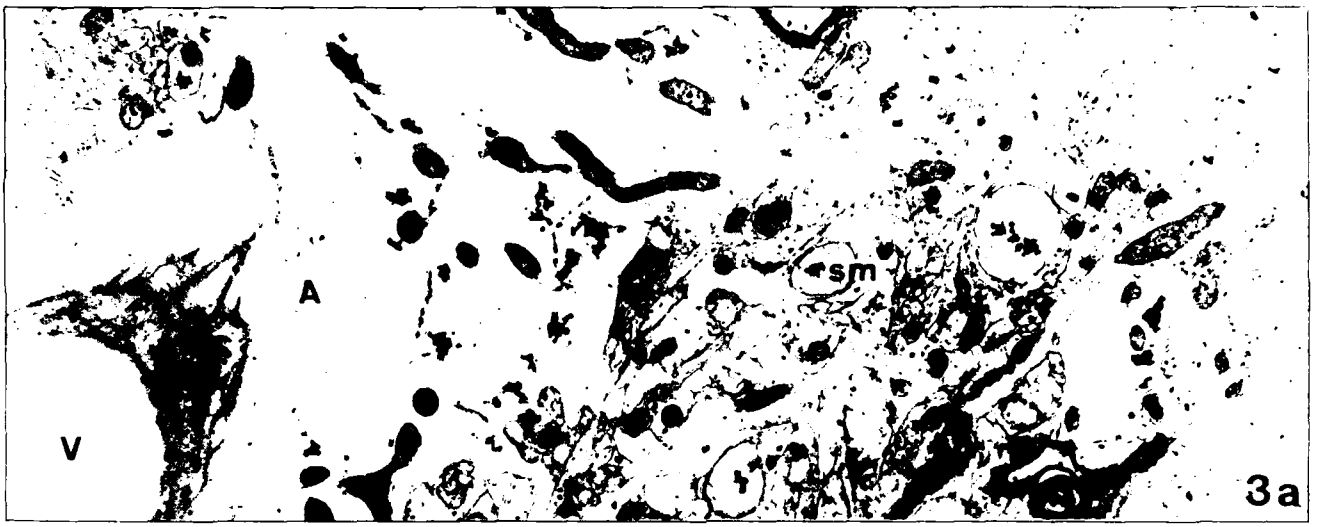
3) Between 30 minutes and two hours, extracellular edema becomes apparent (Figure 3B). At this time, the first signs of presynaptic Ca^{++} accumulation are observed.

4) Between two hours and 24 hours postischemia, a striking increase in presynaptic Ca^{++} becomes visible (Figure 3C). The localization of the Ca^{++} in the stratum radiatum and the asymmetric type of synapses suggest that they belong to excitatory Schaffer collaterals.

5) At the same time, postsynaptic dendrites show the first morphologic signs of irreversible degeneration. Dense, flocculent material is formed at subplasmalemmal sites (Figure 3D). This alteration may be accompanied by diffuse cytosolic Ca^{++} accumulation at the postsynaptic site, and it may be interpreted as a pre-stage of coagulative necrosis.

6) Typical coagulative cell change develops after 24 hours in CA_1 pyramidal cells. Cell organelles are still recognizable and large amounts of Ca^{++} appear in dilated profiles of endoplasmic reticulum (Figure 3E). At the same time, glycogen is abundantly present in astrocytes, which might indicate that glycogenolysis is blocked.

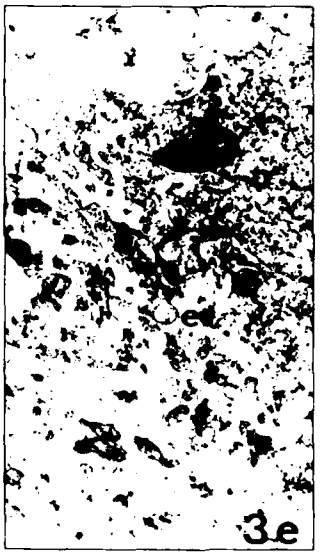
7) After two days, irreversible neuronal necrosis becomes evident. The great majority of CA_1 pyramidal cells show coagulative cell change. Their nuclei are pyknotic, but devoid of Ca^{++}. Nuclear membrane and plasmalemma are visually intact. Mitochondria contain increased Ca^{++}

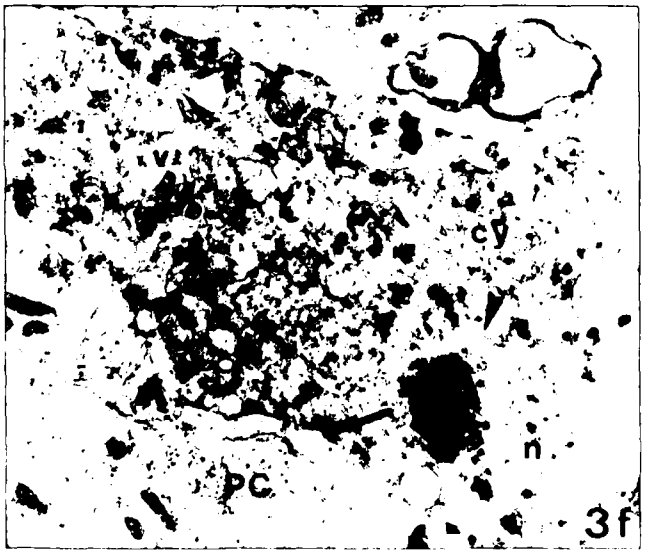

A
V
sm
3a


at
3b


at
3c


d
3d


3e


cy
n
PC
3f

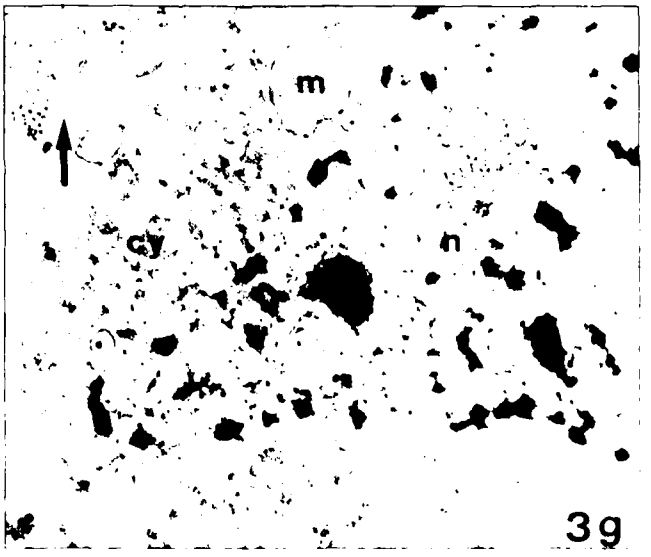

m
cy
n
3g

Fig. 3. *Subcellular Ca^{2+} distribution in the CA_1 hippocampus at different time intervals after eight minutes of incomplete ischemia induced by transient bilateral carotid artery ligation and severe hypotension. Ca^{2+} appears as black precipitates. At one minute before recirculation (A, x 11,750), a considerable part of the mitochondria is heavily swollen (sm) and astrocytes (A) appear edematous. Both are filled with substantial amounts of Ca^{2+} precipitate. Slightly elevated Ca^{2+} content can be found also in normal mitochondria (m). (V = cerebral vessel). At two hours postischemia (B, x 17,550), swelling of mitochondria (m) has completely disappeared. Instead, slight extracellular edema becomes apparent (arrows). At the same time, the first signs of presynaptic Ca^{2+} overload become visible in excitatory axon terminals (at). Ca^{2+} content in mitochondria and synaptic vesicles (s) is comparable to that in normal rats. One day after recirculation (C, x 17,550), presynaptic Ca^{2+} overload is pronounced. A large part of slightly swollen axon terminals (at) are filled with huge amounts of black Ca^{2+} precipitate. Synaptic vesicles (s) remain unchanged, although they tend to be grouped in the central part of the synapse. Mitochondria (m) are slightly swollen. At the same time and more proximal to the CA_1 pyramidal cell bodies (D, x 16,850), flocculent degeneration takes place in dendritic processes (d), in particular at subplasmalemmal sites (arrows). In the pyramidal cell layer (E, x 6,300), the neuronal endoplasmic reticulum (er), as well as some mitochondria (arrowhead), dilate and become filled with large amounts of precipitate. The nucleus of these cells (n) appears normal, with only slightly elevated Ca^{2+} content. A further stage of irreversible injury is seen at three days postischemia (E, x 9,700). Coagulative cell change with pyknosis of nuclei (n) and densification of the cytoplasm (cy) is in sharp contrast with the morphologic picture of normal pyramidal cells (PC). Nuclear membrane (arrow head) and plasma membrane (arrow) of this cell look unaltered. Ca^{2+} has disappeared from the nucleus and is concentrated now in intracytoplasmic vacuoles (v). Finally (G, x 14,200), all cell organelles completely disintegrate. Due to disruption of the plasmalemma (arrow) cytoplasm (cy), nucleus (n), and mitochondria (m) become hydropic and all Ca^{2+} is washed out.*

precipitate, but most of the Ca^{2+} is confined to intracytoplasmic vacuoles that probably are remnants of swollen endoplasmic reticulum (Figure 3F).

8) Later, a visible membrane degradation becomes apparent. Plasma membranes of coagulated cells show clear discontinuities and the cytoskeleton is disorganized. Ca^{2+} precipitates are no longer seen in the cell, with the exception of some vesicles (Figure 3G).

9) Proliferating glial cells fill up the dead space and macrophages eliminate cell remnants. In the extracellular spaces, large Ca^{2+} oxalate crystals may be found. Their presence was interpreted as a possible sign of calcification.[15]

The chain of events described applies to an eight-minute ischemic period in only one type of experimental model. Whether the same progressive degeneration applies also in other situations in which more drastic insults are imposed has not yet been investigated. However, early microvacuolation accompanied by massive but reversible Ca^{2+} accumulation and delayed coagulative necrosis with cytosolic toxic Ca^{2+} overload have been found in hypoxia, incomplete ischemia, and epilepsy models.

Effects of Treatment with Ca^{2+} Entry Blockers

Numerous trials to prevent Ca^{2+} overload and irreversible ischemic brain cell death have been carried out in the past, but with variable success. It is beyond the scope of our discussion to evaluate the results obtained in these investigations.

As an addition to our previous work on the effects of the selective Ca^{2+} entry blocker flunarizine against structural hypoxic damage,[13] we compared its effect with that of nicardipine and diltiazem. Using a hypoxic model as previously described,[13] we found that 24 hours after unilateral carotid artery ligation and exposure to nitrogen, structural damage to the parietal cortex was significantly reduced in rats treated orally four hours before hypoxia with 20 mg/kg flunarizine and with 40 mg/kg nicardipine one hour before hypoxia (Table). Diltiazem (40 mg/kg, one hour before hypoxia and lower doses of nicardipine (1.0 mg/kg and 10 mg/kg, one hour before hypoxia) had no effect. These results correlated well with pharmacological data obtained in different screening tests.[19] Direct drug interference at the cellular level might be necessary to obtain beneficial effects. A drug such as flunarizine, which readily penetrates the blood brain barrier,[20] might fulfill this requirement. For similar reasons, flunarizine might also be able to ameliorate brain damage when used for postischemic treatment.

Prevention of delayed brain injury has been shown in two incomplete ischemia models. A reduction of structural damage to cerebral cells was found in rats treated with 0.1 mg/kg flunarizine at the end of a 20-minute period of 4-VO[15] or after a 9-minute period of 2-VO.[21] Delayed neuronal necrosis was evaluated in the CA_1 hippocampus after survival periods of three days and one week, respectively. Flunarizine had no effect on postischemic CBF in the 2-VO ischemic model (Wieloch, personal communication), which suggests that its mechanism is direct cellular action, such as proposed earlier.[6]

This concept is strengthened by in vitro experiments (offering the advantage of no blood flow and no anesthesia), in which it has been shown that posthypoxic recovery of synaptic activity in the CA_1 area of hippocampal slices was improved by in vitro pretreatment with flunarizine.[19,22]

Nevertheless, the vasoactive properties of flunarizine may not be neglected.[23] Several studies indicate its vascular action. White et al[24] found that flunarizine antagonized delayed hypoperfusion following global ischemia. Recently we have shown an amelioration of ipsilateral CBF in neonatal hypoxic rats pretreated with 20 mg/kg flunarizine (unpublished observations). Next to its well-known antivasoconstrictive properties,[23] flunarizine's inhibition of Ca^{2+}-dependent dopamine release[25] might also contribute to its possible perfusion protection action. In addition, clinical applications of flunarizine in peripheral vascular disease, vertebrobasilar insufficiency, and migraine[26] suggest that, apart from flunarizine's direct action at the neuronal membrane, improvement of microcirculation may also be important in ameliorating functional and structural outcome after ischemia or ischemia related cerebral disease.

Discussion

The neuropathological data presented above correspond well with other data reported in the literature. After ischemia,[12-15] as well as after induction of epileptic seizures,[16] a cellular defense mechanism becomes operative that is characterized morphologically by astrocytic swelling and neuronal microvacuolation. In edematous structures, sequestration of huge amounts of Ca^{2+} is apparent. Soon after insult, all cells regain a normal aspect. Only in selectively vulnerable areas, and only after a delayed maturation period of several hours to several days, can an evolution to irreversible injury be expected.[1,2,17] For the great majority of insults, the common morphological picture of irreversible neuronal necrosis is coagulative cell change with high cytosolic Ca^{2+} accumulation.

This significant phenomenon of delayed neurologic decay also has been recognized in human beings who had progressive neurologic deficit at periods of more than 48 hours postresuscitation.[18] Thus it is of great importance to understand the mechanisms of injury that cause defensive Ca^{2+} sequestration to evolve into irreversible toxic Ca^{2+} overload, and to find out what additional mechanisms mediate injury to brain tissue.

There is convincing evidence that excitatory neurotransmission is involved in selective neuronal necrosis after hypoxia or ischemia.[2,7,9] Many glutamate-binding sites are seen in the hippocampal stratum radiatum,[19] which receives glutamatergic input from Schaffer collaterals. Glutamate-binding sites coincide well with areas of selective vulnerability in the hippocampus.

As we have shown in the 2-VO model, damage originates in postsynaptic dendritic processes of CA_1 pyramidal cells. This observation is in accordance with data reported by Johansen et al,[7] who gave morphological evidence that presynaptic terminals are resistant to ischemia. Interruption of synaptic input by transection of the efferent path may completely abolish lesion formation in CA_1 (Wieloch, personal communication). This observation would provide additional support for the involvement of excitatory neurotransmission in ischemic neuronal necrosis. Release of glutamate is mediated by Ca^{2+} influx,[10,11] and the same ion increases postsynaptic receptor sensitivity.[10,20] We have been able to demonstrate that presynaptic Ca^{2+} accumulation preceded postsynaptic Ca^{2+} overload and subplasmalemmal flocculent degeneration.

We propose that during the long-lasting postischemic hypoperfusion period, Ca^{2+} homeostasis is definitely lost. The Ca^{2+} triggers the release of transmitters, which is accompanied by a subsequent rise in intraterminal free Ca^{2+} concentration.[11] At the postsynaptic site, Ca^{2+}-activated proteinases may uncover additional glutamate receptors, which in turn are the basis of enhanced Ca^{2+} conductance.[11] When this sustained postsynaptic Ca^{2+} overload can no longer be neutralized by normal sequestration mechanisms, a cascade of known Ca^{2+}-dependent degenerative processes may be initiated, including protein and phospholipid degeneration, free fatty acid liberation, and free radical formation.[1]

It appears that neuronal survival can be enhanced by interfering with these mechanisms at an early stage after recirculation. Rothman protected hippocampal neurons in vitro by blocking transmitter release or by blocking excitatory amino acids at postsynaptic sites.[8] Meldrum and coworkers prevented early ischemic brain damage through preischemic treatment with an antagonist of n-methyl-d-aspartate receptors.[9]

When recovery periods are too short, however, density of cell damage may be grossly underestimated. Long-term survival models are needed to permit maturation of irreversible neuronal damage.[2,7] Two studies on long-term recovery show that it seems possible, in the rat at least, to improve neuronal survival after postischemic treatment with the selective Ca^{2+} overload blocker flunarizine.[13,21] Currently we are investigating whether this drug exerts its beneficial effect by prevention of abnormal Ca^{2+} fluxes at the excitatory synapses, either by diminishing presynaptic Ca^{2+} accumulation or by inhibiting postsynaptic Ca^{2+} overload.

TABLE. *Summary of ischemic neuron counts in the cerebral cortex of rats 24 hours after combined ischemic-hypoxic insult*[a]

Treatment Group	N	Rats Without Damage	Dead Rats	Median[b] Cells/mm	P
Solvent[d] 1 hr PO	16	1	0	702 (201-1 130)	
Flunarizine 20 mg/kg 4 h PO	8	6	0	0 (0-819)	0 003
Nicardipine 40 mg/kg 1 h PO	8	3	1	64 (0-664)	0 008
Nicardipine 10 mg/kg 1 h PO	8	2	1	879 (0-10 000)	NS
Nicardipine 1 0 mg/kg 1 h PO	8	0	1	847 (76-2 540)	NS
Diltiazem 40 mg/kg 1 h PO	8	1	0	636 (0-1 489)	NS

[a]Levine preparation; see reference 13
[b]Only surviving animals included; between brackets 95% confidence limits
[c]Mann Whitney U-test (2-tailed); $(P) < .05$; NS = not significant
[d]Solvent: 20% polypropyleneglycol

The authors are grateful to Dr D Ashton for reviewing the manuscript, to M Hasel-donckx and B Van Deuren for their expert technical assistance, to L Leissen for preparing the illustrations, and to Mrs D Verkuringen for typing the manuscript.

References

1. Siesjö BK: Cell damage in the brain: A speculative synthesis. *J Cereb Blood Flow Metab* 1981;1:155-185.

2. Meldrum BS: Metabolic effects of prolonged epileptic seizures and the causation of epileptic brain damage, in Clifford RF (ed): *Metabolic Disorders of the Nervous System*. London, Pitman, 1981, pp 175-187.

3. White BC, Wiegenstein JG, Winegar CD: Brain ischemic anoxia. Mechanisms of injury. *JAMA* 1984;251:1586-1590.

4. Siesjö BK, Wieloch T: Brain ischemia and cellular calcium homeostasis, in Godtraind T, et al (eds): *Calcium Entry Blockers and Tissue Protection*. New York, Raven Press, 1985, pp 139-149.

5. Farber JL: The role of calcium in cell death. *Life Sci* 1981;29:1289-1295.

6. Van Reempts J, Borgers M: Morphological assessment of pharmacological brain protection, in Wauquier A, et al (eds): *Protection of Tissues Against Hypoxia*. Amsterdam, Elsevier, 1982, pp 263-274.

7. Johansen FF, Jorgensen MB, Ekstrom von Lubitz DKJ, et al: Selective dendrite damage in hippocampal CA_1 stratum radiatum with unchanged axon ultrastructure and glutamate uptake after transient cerebral ischemia in the rat. *Brain Res* 1984;291:373-377.

8. Rothman S: Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. *J Neurosci* 1984;4:1884-1891.

9. Simon RP, Swan JH, Griffiths T, et al: Blockade of N-methyl-d-aspartate receptors may protect against ischemic damage in the brain. *Science* 1984;226:850-852.

10. Kudo Y, Oka JI: The role of calcium ion in the L-glutamate-induced depolarization in the frog spinal cord. *Comp Biochem Physiol* 1982;72C:231-236.

11. Burgoyne RD, Cumming R, Geisow MJ: Measurement of free calcium in synaptosomes and the effects of depolarization by potassium and glutamate. *Biochem Soc Trans* 1984;12:806-807.

12. Van Reempts J: The hypoxic brain. Histological and ultrastructural aspects. *Behav Brain Res* 1984;14:99-108.

13. Van Reempts J, Borgers M, Van Dael L, et al: Protection with flunarizine against hypoxic-ischemic damage of the rat cerebral cortex. A quantitative morphologic assessment. *Arch Int Pharmacodyn Ther* 1983;262:76-88.

14. Silverstein F, Johnston MV: Effects of hypoxia-ischemia on monoamine metabolism in the immature brain. *Ann Neurol* 1984;15:342-347.

15. Van Reempts J, Haseldonckx M, Van de Ven M, et al: Morphology and ultrastructural calcium distribution in the rat hippocampus after severe transient ischemia, in Bes A, et al (eds): *Cerebral Ischemia*. Amsterdam, Elsevier, 1984, pp 113-118.

16. Smith MJ, Bendek G, Dahlgren N, et al: Models for studying long-term recovery following forebrain ischemia in the rat. 2. A 2-vessel occlusion model. *Acta Neurol Scand* 1984;69:385-401.

17. Kirino T, Tamura A, Sano K: Delayed neuronal death in the hippocampus following brief ischemia, in Bes A, et al (eds): *Cerebral Ischemia*. Amsterdam, Elsevier, 1984, pp 25-34.

18. Griffiths T, Evans MC, Meldrum BS: Status epilepticus: The reversibility of calcium loading and acute neuronal pathological changes in the rat hippocampus. *Neuroscience* 1984;12:557-567.

19. Wauquier A, Fransen J, Clincke G, et al: Calcium entry blockers are cerebral protecting agents, in Godtraind T, et al (eds): *Calcium Entry Blockers and Tissue Protection*. New York, Raven Press, 1985, pp 163-172.

20. Michiels M, Hendriks R, Knaeps F, et al: Absorption and tissue distribution of flunarizine in rats, pigs and dogs. *Arzneimitteltorsch* 1983;33:1135-1142.

21. Deshpande JK, Wieloch T: Amelioration of ischemic brain damage by postischemic treatment with flunarizine. *Neurol Res* 1985, in press.

22. Ashton D, Edmonds HL, Wauquier A: Recovery of *in vitro* hippocampal slices from hypoxia is improved by flunarizine, abstract. International Symposium on Calcium Entry Blockers and Tissue Protection, Rome, Italy, March 15-16, 1984, p 49.

23. Van Nueten JM: Calcium entry blockers and vascular smooth muscle reactivity, in Godtraind T, et al (eds): *Calcium Entry Blockers and Tissue Protection*. New York, Raven Press, 1985, pp 69-79.

24. White BC, Gadzinski DS, Hochner PJ, et al: Correction of canine cerebral cortical blood flow and vascular resistance after cardiac arrest using flunarizine, a calcium antagonist. *Ann Emerg Med* 1982;11:118-127.

25. Silverstein FS, Buchanan K, Johnston MV: Flunarizine limits striatal dopamine release induced by hypoxia-ischemia, abstract. *Soc Neurosci* 1984;10(Part 1):66.

26. Godfraind T, Vanhoutte PM, Govoni S, et al (eds): *Calcium Entry Blockers and Tissue Protection*. New York, Raven Press, 1985.

27. Smith ML, Auer RN, Siesjö BK: The density and distribution of ischemic brain injury in the rat following 2-10 min of forebrain ischemia. *Acta Neuropathol (Berl)* 1984;46:319-332.

28. White BC, Aust SD, Arfors KE, et al: Brain injury by ischemic anoxia: Hypothesis extension. A tale of two ions. *Ann Emerg Med* 1984;13:862-867.

29. Greenamyre JT, Young AB, Penney JB: Quantitative autoradiographic distribution of L-[^{3}H] glutamate-binding sites in rat central nervous system. *J Neurosci* 1984;4:2133-2144.

30. Baudry M, Siman R, Smith EK, et al: Regulation by calcium ions of glutamate receptor binding in hippocampal slices. *Eur J Pharmacol* 1983;90:161-168.

31. Kusano K, Miledi R, Stinnakre J: Postsynaptic entry of calcium induced by transmitter action. *Proc R Soc B* 1975, 189:49-58.

Information For Authors

EDITORIAL GUIDELINES

The editors invite submissions on matters relevant to emergency medicine and emergency health services. Manuscripts and other editorial communications should be sent to:

The Editor
Annals of Emergency Medicine
PO Box 619911
Dallas, Texas 75261-9911

All submissions accepted for consideration will receive peer review in a prompt, professional, and confidential manner. Submissions are reviewed for possible publication with the understanding that they are original and not simultaneously under consideration by another journal. Accepted manuscripts become the property of *Annals*, and may not be published elsewhere without the written permission of *Annals*.

The covering letter should designate the name, address, and telephone number of a single author for purposes of negotiation regarding the manuscript. It should include a statement that the material proposed for publication is specifically identified, by the author(s), with one of the following categories, according to the guidelines therein.

The editors invite submissions for the following journal categories:

Original Contributions: Original studies of emergency health problems, their etiology, epidemiology, pathology, diagnosis or treatment; investigations and critical analyses of systems of emergency care and the elements or components of those systems. References are required.

Concepts, Components & Configurations: Descriptions of clinical and nonclinical problems and solutions, both proposed and actual, in emergency health services; descriptions of novel or unique approaches to the development, management, provision, or performance of services; formats for emergency health systems and subsystems. Include appropriate references.

Forum: Detailed critical reviews, essays, articles of historical or biographical interest, pertinent contributions from related disciplines. Informal style, when consistent with the content, is invited. Provide appropriate references.

Collective Reviews: Extensive reviews of the literature on a narrow clinical topic. References must include, but need not be limited to, the last three years of literature.

Methods & Techniques: Succinct, didactic articles offering specific methods of approach in well-defined clinical and nonclinical emergency situations, or detailing a special technique applicable to a clearly identified problem. References are invited.

Case Reports: Brief descriptions of emergency problems that are unusual, or routine problems for which a novel therapeutic solution has been devised. Discussion of implications is suggested, and references should be limited to those that are relevant to the case presented.

Correspondence: Observations, opinions, corrections, and comments on topics under discussion in *Annals* or elsewhere; very brief reports of cases or other items of interest. Permission to publish must be granted in postscript.

Guest Editorials: Authoritative comments or opinions on major current problems of emergency physicians, or on controversial matters with significant implications for emergency medicine; qualified, thorough analysis and criticism of articles appearing in *Annals*.

Case Conferences: Emergency medicine residency programs are invited to submit a list of topics for consideration by the Editor prior to preparation of a manuscript.

MANUSCRIPT PREPARATION

Adherence to form appropriate to the purpose of the material is requested. Nomenclature, abbreviations, units, symbols, and other items of usage and style should conform to the recommendations of the most recent issue of *Manual for Authors & Editors* published by the American Medical Association.

Type the manuscript and references double spaced on 8½- × 11-inch heavy-duty paper. Submit one original and four photocopies. Use generous margins – at least 1½ inches at the top, bottom, and left, and one inch at the right. Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables, and legends for tables and figures. Number pages consecutively, beginning with the title page. Type a running head consisting of a shortened form of the title in the upper left corner of each page, and type the page number in the upper right corner. To ensure blinded, impartial review, *do not include the author's name* in the running head.

Title Page: Titling should be short and specific, clear and amenable to indexing. A subtitle may assist in curtailing length. On the title page include the following: 1) the title, 2) the full name, highest academic degrees, and affiliation of each author, 3) name of organization and date of assembly if the article has been presented, 4) acknowledgment of grants (including grant number) or other financial support, and 5) the phrase, "Address for reprints:" followed by the full name and address of the appropriate author.

Abstract and Key Words: On the second page, include an abstract of no more than 150 words that states the purposes of the study, basic procedures, main findings, and principal conclusions. Below the abstract provide three to ten "key words" for use in indexing the article.

Text: Brevity is encouraged. Limit Original Contributions, Concepts, and Forum articles to 25 typewritten pages; limit Methods articles, Case Reports, and Editorials to eight typewritten pages; limit Correspondence to three typewritten pages. When appropriate, divide the text into Introduction, Methods, Results, and Discussion. *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively. *Methods:* Identify the methods, apparatus, and procedures in sufficient detail to allow others to reproduce the results. Reference established methods, including statistical methods. Provide references and brief descriptions for methods that are not well known. Describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. *Results:* Present results in logical sequence in the text, tables, and figures. Do not repeat in the text all the data in the tables or figures. Emphasize or summarize only important observations. *Discussion:* Emphasize new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include the implications and limitations of the findings, and relate observations to other relevant studies. Link conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

References: Number references consecutively in order of their appearance in the text, and list them in numerical order at the end of the manuscript. Include references to unpublished information parenthetically in the text. Reference abbreviations should conform to *Index Medicus* style; for all other style and usage considerations, consult the AMA *Manual for Authors & Editors*. Examples of correct referencing forms are given below:

Journal Article:

Cuddy PG, Elenbaas RM, Elenbaas JK, et al: Evaluating the medical literature, Part I: Abstract, introduction, methods. *Ann Emerg Med* 1983;12:549-555.

Book:

Huth EJ: *How to Write and Publish Papers in the Medical Sciences*. Philadelphia, ISI Press, 1982, p 143-153.

Book Chapter:

Jelenko C: Burns, in Tintinalli JE (ed): *A Study Guide in Emergency Medicine*. Dallas, American College of Emergency Physicians, 1978, vol 2, p 5-1.

Tables: Type tables double spaced on separate sheets with number and title. Omit internal horizontal and vertical rules. Cite each table consecutively in the text.

Figures: Submit an original and four duplicates of glossy, high-contrast prints or original sketches in black ink on white paper. If explanatory markings (arrows, type, etc) are required, do not mark on print or artwork but show exact mark and positioning on a photocopy. Identify each figure on a separate page by number, figure title, manuscript title, and arrow indicating top. *Do not indicate author's name.* Roentgenograms should be submitted as high-contrast, right-reading, glossy prints with black areas of print corresponding with black areas of original negative. Cite each figure consecutively in the text.

Permissions: Any submitted material that has been published elsewhere must be accompanied by the written consent of the author and publisher for reproduction in *Annals*. Photographs of recognizable subjects must be accompanied by a release, signed by the subject or responsible individual, authorizing publication. Clearance to publish, where an institutional requirement, must be supplied. When appropriate, a release form indicating project approval by an institution's human subject review committee must accompany the manuscript.

Author Approval, Reprints: *Annals* is not responsible for statements made by any contributor. Authors should retain copies of all submitted material. All accepted manuscripts are subject to copyediting. Authors will receive for approval an edited typescript that must be returned within seven days of receipt. If not returned within this time, the typescript will be considered approved by the author. No changes will be accepted after the typescript is approved. Authors are responsible for all statements made in the text, including any changes made by the editor or editorial staff. Authors may order reprints after publication. A form for this purpose, with a copy of the Journal in which the article appears, will be sent to corresponding authors at the time of publication. Readers should contact authors to obtain reprints.

Session 2: Cardiopulmonary Resuscitation

An estimated 60% of deaths caused by ischemic heart disease occur within the first hour after coronary occlusion. Cardiopulmonary resuscitation was developed in the 1960s as a method of providing to cardiac arrest victims temporary insufflation of the lungs and partial circulation to vital tissues until an effective heartbeat could be restored. The currently practiced techniques are widely taught, and instructors enforce rigid adherence to specific resuscitation details, such as number of compressions per minute, ventilation rate, sequence, and volume.

In the last several years many investigators have demonstrated that "new" CPR techniques produce considerably higher cardiac output than do the standard techniques now taught by the American Heart Association and the Red Cross. Dr Traystman and his colleagues at Johns Hopkins, for instance, report significantly elevated cardiac output with simultaneous ventilation compression CPR (SVC-CPR). Other closed-chest resuscitation techniques that seem to produce higher cardiac output than does standard CPR include interposed abdominal compression CPR (IAC-CPR) and constant abdominal compression using an abdominal binder such as the MAST garment. Various investigators have proposed changes in timing and duration of chest compression, as well as changes in duration of ventilation. Open-chest CPR seems to provide coronary and carotid blood flows nearer normal than any other compression modality. Despite the apparent advantages of "new" CPR techniques, studies of patient *survival*, such as those conducted by Dr Thompson and his colleagues, have not yet demonstrated a significant difference between "new" and conventional CPR.

Dr Niemann and Dr Cummins emphasize that early defibrillation is clearly the treatment of choice for ventricular fibrillation. The concept of a "therapeutic window" has gained a dominant place in our thinking about cardiac arrest and defibrillation. This concept affirms our clinical experience that successful countershock delivered within ten minutes after the onset of ventricular fibrillation provides the best hope for survival of cardiac arrest. The longer the heart remains ineffective, the smaller the chance of successful resuscitation. This is the conceptual underpinning for the portable or implantable "home or office" computerized defibrillation devices described by Dr Cummins.

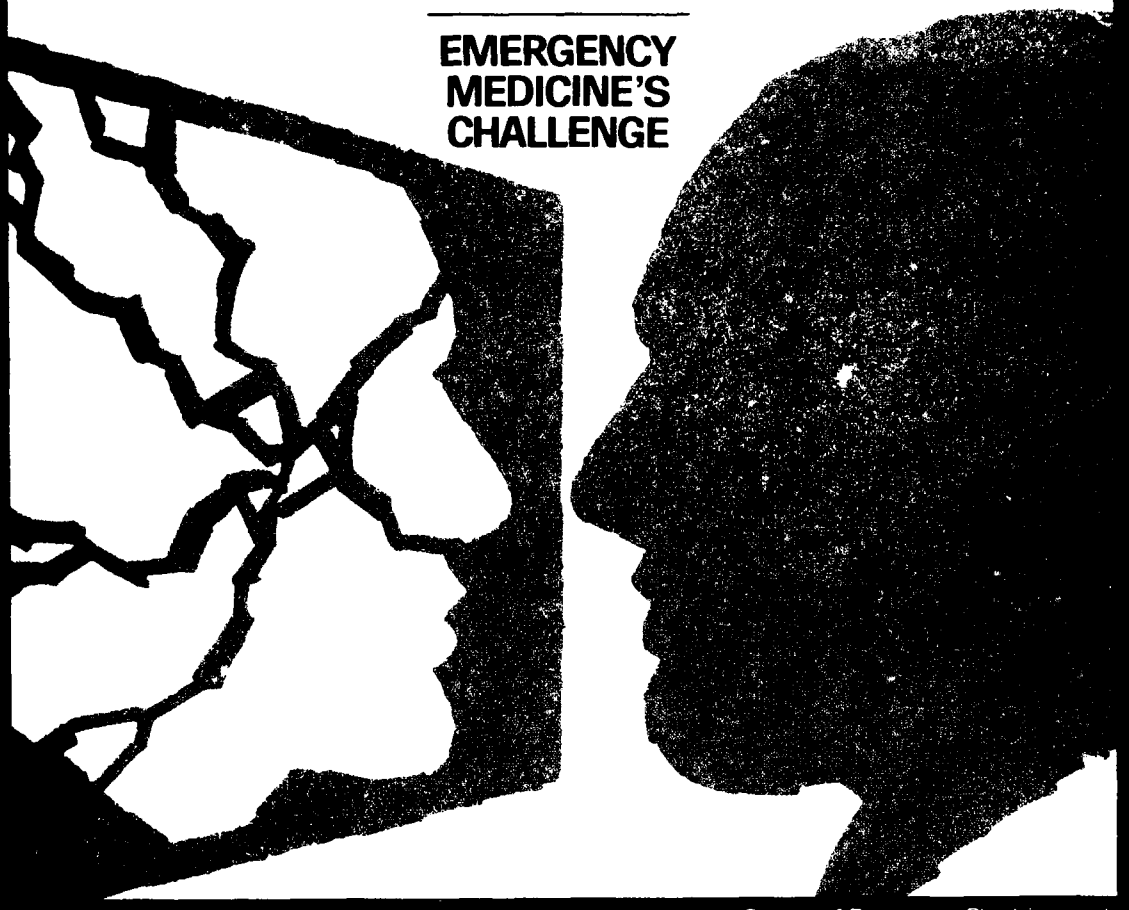
Dr Niemann emphasizes that CPR research must be directed to the real clinical problems we face. Researchers must begin to try to provide clinicians with answers to questions such as these: What should we teach bystanders who respond to cardiac arrest? What is the role of computerized defibrillation? What procedures should be undertaken by paramedics, emergency physicians, and intensive care unit staff to maximize a victim's cardiac and cerebral recovery?

In this regard, our discussion perhaps yielded more questions than answers. Our resuscitative techniques can certainly be improved, but the specific steps toward that end are still somewhat unclear. The general areas of cardiac and cerebral resuscitation have been, and will continue to be, important areas of investigation for research in emergency medicine.

Douglas A Rund, MD, FACEP
Associate Professor and Director
Division of Emergency Medicine
Department of Preventive Medicine
The Ohio State University College of Medicine
Columbus, Ohio

THE SUICIDE EPIDEMIC:

EMERGENCY MEDICINE'S CHALLENGE



A new continuing medical education program developed by the American College of Emergency Physicians and the Emergency Medicine Foundation is now available to help emergency care providers:

identify and manage a suicide attempt
assess the risk of a repeated attempt
determine appropriate patient referral and disposition

A 20-minute videotape and monograph produced in consultation with Douglas Rund, MD, FACEP, and Pat Harvey, MD

The monograph includes risk charts

Approved for 2 hours of AMA Category I and ACEP Category I credit

($10 for ACEP members, $20 for non-members)

AMERICAN COLLEGE OF EMERGENCY PHYSICIANS

[illegible]

____ ¾" video cassette
____ ½" Beta video cassette
____ ½" VHS video cassette
____ Total number of copies

Enclosed is my payment of $_____ Payment must be remitted in US funds only
(TX residents add 5⅛% sales tax)
Prepayment is required.

[illegible]

AR _____

BT _____

NA _____

Please allow 4-6 weeks for delivery.

SPECIAL CONTRIBUTION
brain blood flow, CPR, epinephrine, myocardial blood flow

Beneficial Effect of Epinephrine Infusion on Cerebral and Myocardial Blood Flows During CPR

It is hypothesized that epinephrine improves the ability to resuscitate the heart through a mechanism thought to be related to the increase in aortic pressure. Our results with epinephrine infusion during CPR are consistent with this hypothesis. Epinephrine selectively increased vascular resistance in noncerebral, noncoronary vascular beds, as indicated by a decrease in microsphere-determined blood flow in these areas. This increased vascular resistance raised aortic pressure during the chest compression phase and the relaxation phase of CPR. Because intracranial and right atrial pressures were only slightly higher with epinephrine, cerebral and myocardial perfusion pressures and blood flows were significantly improved. This beneficial effect (compared to no administration of a vasopressor) was more pronounced as CPR progressed beyond ten minutes. Enhanced cerebral and myocardial perfusion occurred with epinephrine when either the conventional or simultaneous compression and ventilation (SCV) mode of CPR was employed in dogs. Similar selective perfusion was sustained for 50 minutes of SCV-CPR with epinephrine, even when the onset of CPR was delayed five minutes. Regional brain blood flow differed in the delayed-CPR group in that cerebellum, brain stem, and thalamic regions initially had higher blood flows. In an infant animal model of CPR using conventional CPR in piglets, epinephrine also was found to increase cerebral and myocardial blood flows. These results show that administration of epinephrine benefits different age groups of different species with different modes of CPR; that benefits occur even with delayed onset of CPR which is associated with additional anoxia and acidosis; and that epinephrine administration is particularly effective in sustaining cerebral and coronary perfusion during prolonged CPR. [Koehler RC, Michael JR, Guerci AD, Chandra N, Schleien CL, Dean JM, Rogers MC, Weisfeldt ML, Traystman RJ: Beneficial effect of epinephrine infusion on cerebral and myocardial blood flows during CPR. Ann Emerg Med August 1985;14:744-749.]

Raymond C Koehler PhD*
John R Michael MD**
Alan D Guerci MD*
Nisha Chandra MD*
Charles L Schleien MD*
J Michael Dean MD*
Mark C Rogers MD*
Myron L Weisfeldt MD*
Richard J Traystman PhD*
Baltimore Maryland

From the Departments of Anesthesiology Critical Care Medicine* and Medicine** The Johns Hopkins Medical Institutions Baltimore Maryland

Presented at the 1985 UAEM IRIEM Research Symposium in Orlando Florida February 7-8, 1985

Supported by Ischemic Heart Disease SCOR grant P50-HL 17655-07 and by NS 20020 from the NIH

Address for reprints Raymond C Koehler PhD Department of Anesthesiology Critical Care Medicine The Johns Hopkins Medical Institutions 600 North Wolfe Street Baltimore Maryland 21205

INTRODUCTION

A variety of vasopressor agents commonly are employed during cardiopulmonary resuscitation (CPR). Early work by Redding and Pearson[1] and later studies by Yakaitis and colleagues[2] indicated improved incidence of cardiac resuscitation in different animal models of cardiac arrest when either epinephrine or alpha-adrenergic agonists were used. This improvement was related to the increase in aortic pressure that occurred during the relaxation phase of chest compression, which presumably increased coronary blood flow. Such an increase in coronary perfusion is critical because most animal studies report that coronary blood flow is less than 20 mL/min/100 g when vasopressors are not infused during external chest compression.[3-7] We have reported on the degree to which epinephrine infusion increases coronary blood flow in dogs.[8] We review those results and report our more recent work.

We also have assessed the effect of epinephrine infusion on cerebral perfusion. In earlier studies conventional CPR with sternal compression on large dogs produced cerebral blood flows of only 5% of prearrest levels.[6,7] A higher cerebral blood flow rate of approximately 30% of baseline was achieved with simultaneous compression and ventilation (SCV) CPR,[6,7] or with lateral chest wall compression[4] (which probably produces higher intrathoracic pres-

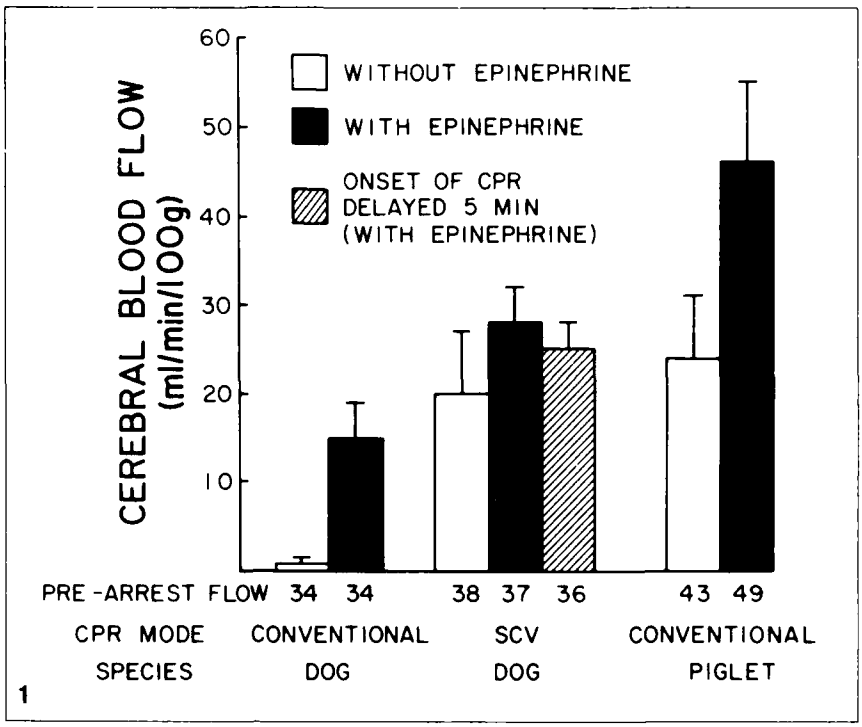


Fig 1. *Cerebral blood flow (mean and SE) during CPR with and without continuous epinephrine infusion. Mean prearrest flows are indicated under the bars for each group.*

sures than does sternal compression in dogs). Internal cardiac massage can produce cerebral perfusion that is 70% to 100% of normal levels,[4,9] but this alternative to external compression is not always feasible. Thus there is ample room for improving cerebral blood flow during external CPR by pharmacological means.

In addition to assessing the effect of epinephrine infusion when CPR is begun shortly after ventricular fibrillation, we addressed the question of whether any beneficial effect prevails under the more realistic circumstance of a five-minute delay before initiation of CPR. It is possible that the anoxia and acidosis associated with such a delay diminishes the efficacy of epinephrine. Also it is known that reperfusing the brain at normal perfusion pressures after global ischemia produces an initial reactive hyperemia, followed by a delayed increase in cerebral vascular resistance.[10] This delayed hypoperfusion cannot be improved simply by increasing arterial pressure with norepinephrine infusion.[10] It is possible, therefore, that with prolonged CPR after five minutes of complete ischemia, cerebral blood flow will fall despite a sustained perfusion pressure with epinephrine.

Epinephrine is routinely used in pediatric CPR. We have developed an animal model of infant CPR in two-week-old piglets. The effectiveness of epinephrine in infant piglets during conventional CPR is compared to the drug's effectiveness in adult dogs.

METHODS

Studies were performed on large (22-kg to 36-kg), adult dogs anesthetized with ketamine (150 mg IM) and pentobarbital (15 to 20 mg/kg IV), and on two-week-old piglets (4-kg to 5-kg) anesthetized with pentobarbital (30 to 40 mg/kg IP). Additional IV pentobarbital was given as needed during surgery. The animals were ventilated through a tracheostomy, and catheters were advanced into the right atrium and thoracic aorta from a femoral approach for pressure measurements. Intracranial pressure was measured from a cannula inserted in the lateral ventricle through a burr hole in the skull. A pacing catheter was placed in the right ventricle from a femoral vein for electrical fibrillation of the heart. Regional blood flow was measured with 15 ± 1 microndiameter radiolabelled microspheres. For the injection of microspheres, a catheter was advanced into the left ventricle from a femoral artery. Arterial reference samples of microspheres were drawn from axillary artery catheters (placed in a subclavian artery) at a rate of 1.9 mL/min during the microsphere injection and for at least five minutes following the injection. We have validated the use of microspheres during CPR,[6] and additional details of the technique have been published elsewhere.[8]

External CPR was performed using a pneumatic piston device (Thumper®, Michigan Instruments). Conventional CPR was performed on dogs at a rate of 60/min, with a 50% duty cycle, and with one breath interposed after every fifth chest compression. In piglets, the recommended rate for infants of 100/min was used, with a duty cycle of 60%. In dogs receiving SCV-CPR, a compression rate of 40/min and a duty cycle of 50% were used. A high airway pressure of 90 mm Hg to 100 mm Hg was applied during the first 40% of each chest compression cycle. Sternal displacement was approximately 20% of the anteroposterior diameter in the dogs subjected to SCV-CPR and in the piglets. Twenty percent displacement was relatively ineffective in large dogs during conventional CPR, however, so compression force was maximized to produce 25% to 30% displacement in this group.

Only one mode of CPR was used during a one-hour period per individual animal. Each animal received either a continuous infusion of epinephrine (4 μg/kg/min) or no epinephrine. At the onset of CPR in the epinephrine groups, a bolus injection of 1.0 mg was administered in the dogs and 50 μg was given in the piglets.

Statistical differences between groups were determined by analysis of variance at the $P < .05$ level.

RESULTS

Conventional CPR in Dogs

Comparisons of cerebral and myocardial blood flows between the animal groups three to six minutes after the commencement of CPR are shown (Figures 1 and 2). In conventional CPR in dogs not receiving epinephrine infusion (n = 7), cerebral and myocardial blood flows were ex-

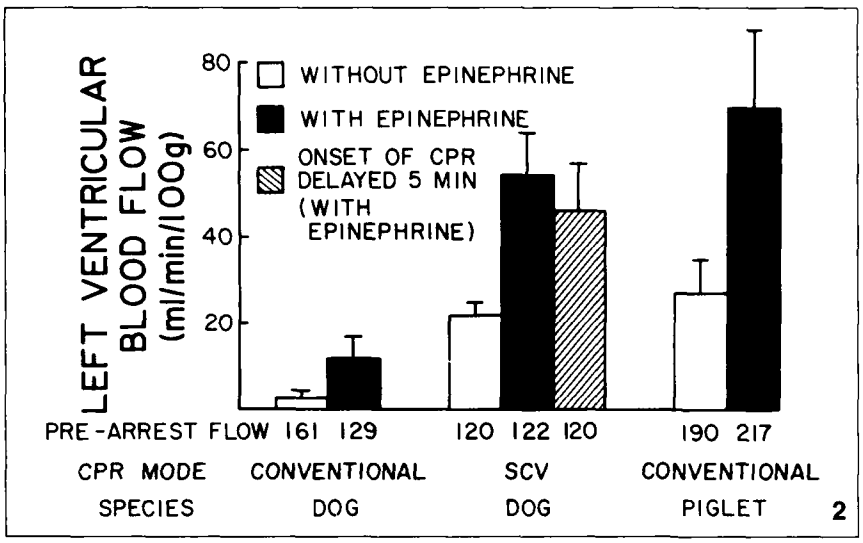


Fig. 2. *Left ventricular blood flow (mean and SE) during CPR with and without continuous epinephrine infusion. Mean prearrest flows are indicated under the bars for each group.*

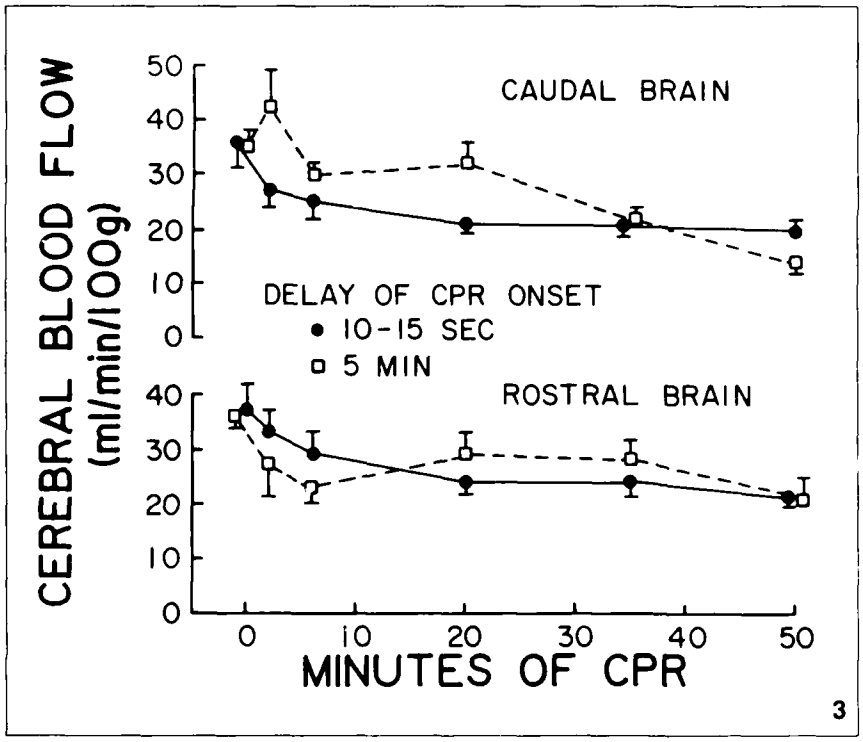


Fig. 3. *Comparison of the effect of a five-minute delay and a short delay (10 to 15 seconds) in the onset of SCV-CPR (both with epinephrine) on blood flow to caudal and rostral brain. Caudal brain region responses (cerebellum, medulla, pons, midbrain, diencephalon, caudate nucleus, and piriform lobe) differed individually between the two groups and were pooled for simplicity. Rostral brain regions (occipital, temporal, parietal, and frontal lobes) responded similarly between the two groups of dogs. Values at time zero are the prearrest means and SE.*

tremely low. With continuous epinephrine infusion (n = 6), perfusion of these organs was significantly higher ($P < .01$). The greater cerebral blood flow observed with epinephrine infusion during conventional CPR was related to a higher mean arterial pressure (43 ± 8 [± SE] vs 22 ± 1 mm Hg), rather than to a lower downstream intracranial pressure (25 ± 3 mm Hg with epinephrine vs 17 ± 1 mm Hg without epinephrine).

SCV-CPR in Dogs

Cerebral and myocardial blood flows were higher with SCV-CPR than with conventional CPR in dogs. Use of epinephrine during SCV-CPR further augmented cerebral blood flow (75% of prearrest) and left ventricular blood flow (44% of prearrest). These higher blood flows were the result of higher perfusion pressures with epinephrine.

Mean aortic pressure was greater with epinephrine (59 ± 3 mm Hg, n = 6) than without epinephrine (40 ± 2 mm Hg, n = 3); and mean intracranial pressure was 28 ± 1 mm Hg in the epinephrine group and 23 ± 4 mm Hg in the nonepinephrine group. Aortic pressure was higher in the epinephrine group during the compression phase (by 16 mm Hg) and during the relaxation phase (by 12 mm Hg). The aortic to right atrial pressure gradient during the chest relaxation phase was greater with epinephrine (27 ± 3 vs 14 ± 1 mm Hg) after six minutes of SCV-CPR.

Aortic and carotid arterial pressures fell substantially after 20 minutes of SCV-CPR in the nonepinephrine group, with little change in right atrial or intracranial pressures. In contrast, perfusion pressures remained stable over a one-hour period in the epinephrine group. This resulted in a widening of the difference in cerebral and myocardial blood flows between the nonepinephrine and epinephrine groups after six minutes of SCV-CPR.

Delayed Onset of CPR

In the preceding experiments, CPR usually was begun within 10 to 15 seconds of ventricular fibrillation. To ascertain whether the beneficial effect of epinephrine prevails when the onset of CPR is delayed, SCV-CPR with continuous epinephrine infusion was started five minutes after inducing fibrillation in another group of dogs (n = 6). In this group with five minutes of complete ischemia, mean

apparently resulted in intra-
ic vascular pressures that were
comparable to those achieved
SCV-CPR in dogs. Switching
conventional CPR to SCV-CPR
h airway pressure (70 mm Hg) in
pilot experiments on piglets pro-
only a slight increase in intra-
ic vascular pressures. This sug-
that the pressure generated with
ntional CPR in piglets is already
and that applying a high airway
ure provides little additional in-
e. There is also a greater pos-
y of direct cardiac and vascular
pression in the piglet given the
e of chest deformation observed.
thout epinephrine (n = 8), cere-
nd myocardial blood flows were
and 17% of prearrest levels, re-
ively, after five minutes of con-
ional CPR. During prolonged
however, aortic pressure fell, and
ral and myocardial blood flows
ached zero levels by 50 minutes.
epinephrine infusion (n = 8),
ral blood flow (approximately
of prearrest) and myocardial
flow (37% of prearrest) were sig-
ntly greater than in the nonepi-
rine group at five minutes ($P <$
and remained higher with pro-
ed CPR. There were no dif-
ces in mean intracranial or right
l pressures between the two
ps, but aortic diastolic pressure
greater in the epinephrine group.
n adult dogs, the higher cerebral
myocardial blood flows with epi-
rine in piglets were due to higher
sion pressures.

CUSSION

ne results of these studies indicate
use of epinephrine improves cere-
and myocardial perfusion in two
rent modes of CPR, conventional
SCV; with a five-minute delay in
onset of CPR; and in an infant
nal model of CPR. The mecha-
n of the beneficial effect of epi-
rine appears to be the same in
of the models. Epinephrine in-
ses systemic vascular resistance
referential vasoconstriction of
cerebral cephalic beds (muscle,
uel and abdominal organs (kidney,
stines).[5] Within each model, car-
output is essentially limited by
capacity of the particular pump
hanism used, so the increase in
emic vascular resistance acts to
perfusion pressure for the heart
brain. Thus epinephrine acts to
redistribute the limited cardiac output.

The beneficial effect on coronary and cerebral perfusion probably occurs during both the compression and relaxation phases of the cycle. During relaxation, when the aortic valve closes, the increase in peripheral resistance appears to increase the time constant for arterial run-off, thereby increasing the aortic to right atrial and aortic to intracranial pressure gradients. During chest compression, the time constant for discharging blood out through the arterial system is prolonged to such a degree that aortic "systolic" pressure can be higher than right atrial "systolic" pressure (ie, aortic pressure approaches intrathoracic pulse pressure instead of aortic "systolic" pressure equalling intrathoracic "systolic" pressure). Thus there may be forward coronary flow during the compression phase in this situation, and the "diastolic" aortic to right atrial pressure gradient may not be completely indicative of coronary flow.

We found that maintaining left ventricular blood flow at levels greater than 20 mL/min/100 g was required for successful defibrillation after one hour of CPR, and that normal brain electrical activity was correlated with cerebral blood flow greater than 15 to 20 mL/min/100 g.[8] Other models of brain ischemia[11] also indicate that electrical function is impaired below these blood flow levels, and that cellular depolarization occurs below a lower cerebral blood flow threshold of approximately 10 mL/min/100 g. Our results with SCV-CPR in dogs and conventional CPR in piglets indicate that cerebral and coronary perfusion are near these thresholds during five to 20 minutes of CPR, but decline with prolonged CPR. Use of epinephrine, however, sustained perfusion above these thresholds for longer periods. Ralston et al[12] have shown that intrapulmonary administration of epinephrine improved coronary and cerebral blood flow during CPR, and improved the ability to resuscitate after prolonged CPR. These findings serve to emphasize the importance of epinephrine administration, particularly with prolonged CPR.

That is not to say that epinephrine is the only vasopressor of choice for resuscitation. Pure alpha-adrenergic agonists also appear to be effective in resuscitating the heart.[12] In addition,

it has been suggested that beta-adrenergic stimulation from epinephrine may have deleterious effects on the subendocardium when coronary blood flow is low and oxygen demand is increased.[13] The question then arises whether the increased myocardial blood flow with epinephrine outweighs any increase in oxygen demand. In one study, it is reported that epinephrine is superior to phenylephrine in terms of myocardial blood flow, although the drugs were not compared at equipressor doses.[14] Another study indicates that myocardial lactate levels may not be improved by epinephrine.[15] Thus it is not clear at present whether epinephrine or pure alpha-adrenergic agonists are of greater benefit for cardiac resuscitation.

The similar question of whether epinephrine stimulates metabolism arises concerning the brain. Circulating catecholamines normally do not increase cerebral blood flow and metabolism unless the blood-brain barrier is disrupted.[16,17] There is some evidence that blood-brain barrier function can be impaired after resuscitation,[18] and that a propranolol-sensitive hypermetabolism can occur during reperfusion after cerebral ischemia.[19] Whether circulating epinephrine stimulates cerebral oxygen demand in the setting of CPR has not been evaluated. Preliminary data from superior sagittal sinus blood samples in piglets indicate that the higher level of cerebral blood flow with epinephrine is associated with a lower level of cerebral oxygen extraction. This suggests that improved cerebral blood flow outweighs any potential metabolic stimulatory effect in terms of tissue oxygenation, compared to no infusion of epinephrine.

We considered the possibility that a five-minute delay in commencing CPR would result in some loss in the effectiveness of epinephrine to sustain higher myocardial and cerebral perfusion pressures and blood flows. This was not the case. In addition, studies of cerebral reperfusion at normal perfusion pressures after complete ischemia have demonstrated the presence of a delayed hypoperfusion that is resistant to norepinephrine-induced increases in arterial pressure.[10] Thus one might expect a gradual decrease in blood flow to the cerebrum with prolonged CPR after five minutes of complete ischemia, despite a sustained perfusion pressure of approximately 30 mm Hg. We found no evidence for delayed hypoperfusion in the cerebrum after 50 minutes of reperfusion (Figure 3). Perhaps the hypoperfusion phenomenon appears only at higher perfusion pressures or with longer reperfusion periods. Also, reperfusion is thought to be quite heterogeneous at the microcirculatory level, which may not be detected by the microsphere technique.[20]

One might also expect five minutes of complete cerebral ischemia (compared to the 10 to 15 seconds usually taken to establish CPR after fibrillation) to produce a larger hyperemic response. This was not evident within the cerebrum after two minutes of CPR, presumably because the vascular bed was maximally dilated at a cerebral perfusion pressure of 30 to 35 mm Hg. In addition, only five seconds of cerebral ischemia can produce maximal peak reactive hyperemia.[21]

In contrast to the cerebrum, caudal areas had higher blood flows for 20 minutes of reperfusion after delayed CPR. Blood flow to brain stem regions initially increased above prearrest levels. Models of cerebral ischemia in rats also show that reperfusion is greater in certain caudal areas, such as in the cerebellum and in discrete brain stem nuclei.[20] Infusion of catecholamines, particularly after opening the blood-brain barrier, can also produce a caudal-rostral redistribution of regional cerebral blood flow in rats without preexisting cerebral ischemia.[17] Thus the caudal-rostral redistribution seen with delayed CPR probably was the result of prolonged ischemia (which may further impair blood-brain barrier function), and probably the effect was then accentuated by epinephrine infusion. The importance of this effect on neurological outcome after cardiac resuscitation currently is not clear.

CONCLUSION

These data demonstrate the effectiveness of epinephrine in increasing cerebral and myocardial blood flows when conventional CPR or SCV-CPR is employed and when CPR is begun within 15 seconds or delayed for five minutes. Results in infant piglets support the use of epinephrine in pediatric CPR, and demonstrate that the efficacy of epinephrine is not unique to the adult dog.

The question of whether potential adverse effects of beta-adrenergic stimulation on myocardial and cerebral metabolism offset the beneficial increase in blood flow is unresolved. Although the use of pure alpha-adrenergic agonists has been suggested,[1,2] the possibility of coronary and cerebral vasoconstriction with these agents also must be considered. Beta$_2$-adrenergic coronary vasodilation,[22] which potentially could counteract alpha-adrenergic constriction, may yet render epinephrine as the vasopressor of choice during CPR.

REFERENCES

1. Redding JS, Pearson JW: Resuscitation from ventricular fibrillation. *JAMA* 1968; 203:93-98.

2. Yakaitis RW, Otto CW, Blitt CD: Relative importance of alpha and beta adrenergic receptors during resuscitation. *Crit Care Med* 1979;7:293-296.

3. Bellamy RF, DeGuzman LR, Pedersen DC: Coronary blood flow during cardiopulmonary resuscitation in swine. *Circulation* 1984;69:174-180.

4. Byrne D, Pass HI, Neely WA, et al: External versus internal cardiac massage in normal and chronically ischemic dogs. *Am Surg* 1980;46:657-662.

5. Ditchey RV, Winkler JV, Rhodes CA: Relative lack of coronary blood flow during closed-chest resuscitation in dogs. *Circulation* 1982;66:297-302.

6. Koehler RC, Chandra N, Guerci AD, et al: Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. *Circulation* 1983, 67:266-275.

7. Luce JM, Ross BK, O'Quin RJ, et al: Regional blood flow during cardiopulmonary resuscitation in dogs using simultaneous and nonsimultaneous compression and ventilation. *Circulation* 1983,67:258-265.

8. Michael JR, Guerci AD, Koehler RC, et al: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984,69:822-835.

9. Staduhar K, Steinberg R, Sotosky M, et al: Cerebral blood flow and common carotid artery blood flow during open chest cardiopulmonary resuscitation in dogs, abstract. *Anesthesiology* 1983;59: A117.

10. Nemoto EM, Snyder JV, Carroll RG, et al: Global ischemia in dogs: Cerebrovascular CO_2 reactivity and autoregulation. *Stroke* 1977;6:42-51.

11. Astrup J, Symon L, Branston NM, et al: Cortical evoked potential and extracellular K^+ and H^+ at critical levels of brain ischemia. *Stroke* 1977;8:51-57.

12. Ralston SH, Voorhees WE, Babbs CF: Intrapulmonary epinephrine during prolonged cardiopulmonary resuscitation: Improved regional blood flow and resuscitation in dogs. *Ann Emerg Med* 1984; 13:79-86.

13. Livesay JJ, Follette DM, Fey KH, et al: Optimizing myocardial supply/demand balance with adrenergic drugs during cardiopulmonary resuscitation. *J Thorac Cardiovasc Surg* 1978;76:244-251.

14. Holmes HR, Babbs CF, Voorhees WD, et al: Influence of adrenergic drugs upon vital organ perfusion during CPR. *Crit Care Med* 1980;8:137-140.

15. Ditchey RV: High-dose epinephrine does not improve the balance between myocardial oxygen supply and demand during cardiopulmonary resuscitation in dogs, abstract. *J Am Coll Cardiol* 1984; 3:596.

16. Abdul-Rahman A, Dahlgren N, Johansson BB, et al: Increase in local cerebral blood flow induced by circulating adrenaline: Involvement of blood-brain barrier dysfunction. *Acta Physiol Scand* 1979;107:227-232.

17. Edvinsson L, Lacombe P, Owman C, et al: Quantitative changes in regional cerebral blood flow of rats induced by alpha- and beta-adrenergic stimulants. *Acta Physiol Scand* 1979;107:289-296.

18. Arai T, Watanabe T, Nagaro T, et al: Blood-brain barrier impairment after cardiac resuscitation. *Crit Care Med* 1981;9: 444-448.

19. Nemoto EM, Hossmann KA, Cooper HK: Post-ischemic hypermetabolism in cat brain. *Stroke* 1981;12:666-676.

20. Kagstrom E, Smith ML, Siesjo BK: Local cerebral blood flow in the recovery period following complete cerebral ischemia in the rat. *J Cereb Blood Flow Metab* 1983;3:170-182.

21. Gourley JK, Heistad DD: Characteristics of reactive hyperemia in the cerebral circulation. *Am J Physiol* 1984; 246:H52-H58.

22. Domenech RJ, MacLellan PR: Transmural ventricular distribution of coronary blood flow during coronary B2-adrenergic receptor activation in dogs. *Circ Res* 1980;46:29-36.

Erratum

In the article by Curry et al, entitled "The Effects of Toxic Concentrations of Theophylline on Oxygen Consumption, Ventricular Work, Acid Base Balance, and Plasma Catecholamine Levels in the Dog" [June 1985;14:554-561], the dosage of epinephrine given on page 559 should have read "1,830 pg/mL of epinephrine (10^{-8}M)," not "1,830 pg mL of epinephrine (10-8M). In Figure 5, the vertical axis of the second graph should have read "$\dot{V}O_2$, (mL O_2, min m^{-2})," not "QO_2, (mL O_2, min m^{-2})."

SPECIAL CONTRIBUTION
CPR; EMS systems; resuscitation

Comparison of Clinical CPR Studies in Milwaukee and Elsewhere in the United States

As we mark the 25th anniversary of the clinical application of closed-chest cardiopulmonary resuscitation (SCPR), it is time to look back and analyze the progress we have made in the resuscitation of sudden death syndrome. Recent studies of SCPR's effectiveness have yielded mixed results, in comparison to early studies that were universally favorable. The continued toll of neurologic injury following SCPR resuscitation, and reinforcement of the importance of defibrillation in resuscitation, stimulate us to find improved forms of SCPR and improved methods of resuscitation delivery in emergency medical systems. [Thompson BM, Stueven HA, Mateer JR, Aprahamian CC, Tucker JF, Darin JC: Comparison of clinical CPR studies in Milwaukee and elsewhere in the United States. Ann Emerg Med August 1985;14: 750-754.]

Bruce M Thompson, MD
Harlan A Stueven, MD
James R Mateer, MD
Charles C Aprahamian, MD
John F Tucker, MD
Joseph C Darin, MD
Milwaukee, Wisconsin

From the Section of Trauma and Emergency Medicine, Medical College of Wisconsin, and the Milwaukee County Medical Complex, Milwaukee, Wisconsin

Presented at the 1985 UAEM IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985

Address for reprints: Bruce M Thompson, MD, Section of Trauma and Emergency Medicine, Milwaukee County Medical Complex, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226

INTRODUCTION

There is little doubt that standard closed-chest cardiopulmonary resuscitation (SCPR) represents a body of knowledge that can be taught, learned, and applied. The critical question is whether the application of SCPR principles can and does affect the outcome of patients suffering from prehospital cardiac arrest.

The impetus for general application of SCPR occurred in the 1970s with the advent of emergency medical services (EMS). Promotion of SCPR was supported by data from Seattle, where there was a lay SCPR program and a tiered EMS paramedic program capable of providing early advanced life support (ALS) effectively.[1,2] The improved results achieved with SCPR in this system in patients presenting with ventricular fibrillation (VF) provided television appeal (*60 Minutes, Emergency*), and were instrumental in the development of nationwide efforts to train the general public in the technique of SCPR.

Early studies[3-8] preceded the development of data collection systems with acceptable resuscitation outcome endpoints, ie, hospital discharge and neurologic survival. Lack of clarity and precision in language used to report SCPR study results and patient selection criteria are also a problem. All patients do not suffer the same type of cardiac arrest: preexisting disease, prearrest medications, arrest time before initiation of SCPR or ALS (or both), and presenting rhythm vary. Patient selection bias within a specific EMS system may preclude patients from entering the EMS data system or bar them from treatment initiated in the field at all. We agree with Polinitsky et al[9] and Eisenberg et al[10] that there has not been enough attention to detail in evaluating and reporting these data.

CLINICAL SCPR STUDIES

Most prehospital clinical studies include entry data (whether the arrest was witnessed, performance of SCPR, estimates of the arrest time) and exit data (successful initial resuscitation, hospital discharge and, more recently, neurologic outcome), but often there is failure to control for the multiple factors that occur between entry and exit. The significant factors and cofactors relating to underlying disease states may be numerous and very important to final outcome.[11] Valid data comparisons probably are possible only when EMS system designs are comparable and when response times are nearly equal. Most investigators have looked for overall differences in resuscitation groups after a number of ALS protocol manipulations were tried.[11]

aortic pressure (59 ± 4 mm Hg), intracranial pressure (33 ± 3 mm Hg), and the aortic to right atrial diastolic gradient (26 ± 3 mm Hg) were essentially the same as those of the epinephrine-SCV-CPR group that had no delay before the commencement of resuscitation. Myocardial and total brain blood flows were similar in the two groups after six minutes and for the remainder of the one hour of CPR. There were regional differences along the neuroaxis of the brain, however, and these differences were a function of duration of CPR (Figure 3).

With the delayed onset of CPR, regions in the caudal portion of the neuroaxis, particularly the cerebellum, medulla, pons, midbrain and diencephalon, had higher blood flows when measured at two, six, and 20 minutes, but lower blood flows after 50 minutes of CPR compared to the group without prolonged ischemia ($P < .01$). After two minutes of SCV-CPR in the ischemic group, blood flow to the medulla, pons, and midbrain actually increased by 70%, 75%, and 53% above prearrest values, respectively. In contrast blood flow to the rostral brain, which represents cerebrum, decreased from prearrest levels after two minutes of CPR and remained essentially unchanged with prolonged CPR (Figure 3). There was no significant difference between the two groups in blood flow to the cerebrum. We conclude that epinephrine can sustain cerebral perfusion after a five-minute delay in the onset of SCV-CPR. A global hypoperfusion phenomenon resistant to epinephrine-induced increases in perfusion pressure was not apparent between groups during the 50 minutes of reperfusion.

Conventional CPR in Piglets

Conventional CPR on infant piglets required much less piston force (approximately 140 newtons) to achieve 20% sternal displacement (2 to 2.5 cm) than was required for adult dogs (540 newtons). There was, however, less recoil of the chest, resulting in a 20% deformation of the anteroposterior diameter during the relaxation phase. Systolic aortic and right atrial pressures in excess of 80 mm Hg were achieved during compression. Thus the 20% displacement was superimposed on a 20% permanent deformation and produced a different chest configuration than that produced by conventional CPR in large, adult dogs. This apparently result
thoracic vascular pressu
more comparable to th
with SCV-CPR in dog
from conventional CPR
at high airway pressure (
a few pilot experiments
duced only a slight inc
thoracic vascular pressu
gests that the pressure
conventional CPR in pi
high, and that applying
pressure provides little
crease. There is also
sibility of direct cardia
compression in the pi
degree of chest deform

Without epinephrine
bral and myocardial bl
50% and 17% of prea
spectively, after five m
ventional CPR. Dur
CPR, however, aortic p
cerebral and myocard
approached zero levels
With epinephrine in
cerebral blood flow
100% of prearrest) a
blood flow (37% of pr
nificantly greater thar
nephrine group at fiv
.01), and remained h
longed CPR. Ther
ferences in mean int
atrial pressures be
groups, but aortic d
was greater in the ep
As in adult dogs, th
and myocardial bloo
nephrine in piglets w
perfusion pressures.

DISCUSSION

The results of thes
that use of epinephr
bral and myocardial
different modes of C
and SCV; with a fiv
the onset of CPR;
animal model of C
nism of the benefi
nephrine appears t
each of the model
creases systemic v
by preferential va
noncerebral ceph
tongue and abdom
intestines).[8] Withi
diac output is ess
the capacity of th
mechanism used,
systemic vascular
raise perfusion pr
and brain. Thus

SCPR was advocated as a means to keep the heart in a state from which it could be resuscitated.[1-3] Recently, however, there has been a general recognition of the limited effectiveness of prehospital SCPR without prompt defibrillation.[12] Enns et al[13] demonstrated the deterioration of cardiac rhythm from ventricular tachyarrhythmias to asystole during Holter monitoring of patients in cardiac arrest when only SCPR was available. On the other hand, there is nearly universal agreement on the effectiveness of electrical defibrillation for VF.[3,8,10,18]

Studies in the Milwaukee Paramedic System

The Milwaukee County Paramedic System is a multi-tiered advanced life support system based on the Seattle model. Basic emergency medical technicians (EMTs) on fire rescue squads and in fire engine companies respond first (first responders; system average, 2.1 minutes), followed by ALS paramedic teams (system average, 6.0 minutes). On-line medical control is performed by a single base station that has multiplex voice radio and continuous electrocardiograph (ECG) telemetry. Staff members of the paramedic base are a small group of ALS-certified physicians on the faculty of the Medical College of Wisconsin. The base physicians follow American Heart Association guidelines for ALS.[11] Paramedics may, however, administer as many as four countershocks for VF prior to contact with the base physician or administration of medications. Data from all paramedic runs are recorded on standard forms and entered in a computer for retrieval and analysis. In addition, all original records and rhythm strips are kept on file for verification of data.

Early evaluation of patients treated in this system who were found in asystole or electromechanical dissociation has showed no significant benefit from bystander SCPR (unpublished data).

Using this mature EMS system, we sought to isolate the effect of the performance of SCPR from other ALS techniques by studying patient response to SCPR or "quick-look" defibrillation (or both) before the administration of other ALS modalities. The effect of bystander SCPR in the prehospital setting was assessed separately from factors such as undocu-
mented "down ti
drug and other the
called for in the A

From January 19
studied 421 consec
suffered a witnesse
arrest, who had an
coarse VF, and wh
the Milwaukee C
System.[14] Pediatric
soming patients and
IV or endotracheal
defibrillation an
Groups of patien
SCPR from a prot
(physician, nurse,
ceived SCPR from
who received no by
compared. A succes
was recorded when
to the administrati
produced an effecti
with pulses.

Of the 363 patien
analysis, 88 (24%) c
initial defibrillation
defibrillation rate w
izen-bystander-SCP
in the no-bystande
significant differen
eighty-six of the 3
were admitted to a
cy department w
a pulse (a success
Ninety-seven of t
were discharged al
tal (a save). The c
SCPR groups had a
tation rate of 51%
26%; the no-byst
also had a success
of 51%, and a sav
rologic outcome c
able. We were un
demonstrate any
effect from byst
Milwaukee para
patients present
rhythm of coarse

Another interes
study was that pa
verted successfu
defibrillation alon
ly to be successf
of 88, 90%) and c
the hospital (54 c
patients who re
vanced cardiac li
(per ALS protoco
tion of prolonge
107 of 275 or 3
charged, 43 of 27
Clearly, electrica
most effective

hence from the study population) because a first responder or a paramedic determines that the patient is dead on the scene. Resuscitation exclusion criteria in Seattle and in most other prehospital systems are not reported. Although spokesmen for many systems claim that American Heart Association guidelines are followed, these guidelines are very conservative and list very few criteria for death (decapitation, rigor mortis, decomposition, and dependent lividity).[11] The actual criteria used in a system to decide on initiation of SCPR may be poorly defined or loosely enforced. The decision may be made not to begin resuscitation on patients who have a small chance of survival, thus rates of resuscitation are increased by treatment only of "healthy" patients.

A study by Roth et al[9] of the Pittsburgh system found a nonresuscitation exclusion of 53% for the 598 people identified as having sustained cardiac arrest during the study period. Only 252 patients (47%) received a resuscitation attempt. Three hundred seventeen patients (53%) were classified as dead on scene because they had no vital signs and because no first responder had initiated SCPR. Although it would be unwise to force a system to attempt complete resuscitation on every cardiac arrest patient, exclusion criteria should be defined, and the total number of cardiac arrest patients for which an EMS response is requested should be documented to allow comparison. We have studied the exclusion bias of the Milwaukee County Paramedic System and found it to be 30% of total arrest responses.[10] Analysis of these data may permit specific exclusion criteria to be developed.

A second factor that may contribute to variable study results is that a rapid response, tiered paramedic system may show no evidence of significant advantage for bystander SCPR because the EMS system intervenes rapidly within a critical period after arrest. None of the studies in the literature reports as rapid a first response EMT time as Milwaukee's, where a system response time of 2 1 minutes[6] from time of telephone call to EMT arrival is nearly identical to the estimated time to initiation of SCPR (1 9 minutes) by bystanders who notify the EMS system in Seattle. If there is a narrow "window" of resuscitability, Milwaukee's first responders may reach arrest victims within that period. In light of this, a community might elect to spend funds to provide a more rapid response system for quick defibrillation, instead of for SCPR classes for its citizens, to achieve equal or even improved results.

A third factor contributing to varied study results is found in recent reports that show an inability of closed-chest SCPR to maintain ventricular fibrillation even for a short period of arrest time.[13] Two studies of prompt EMT defibrillation show improved hospital admission and discharge rates.[12,13] Although it still may be important to teach the steps of SCPR to the public, rapid defibrillation by EMT-Ds or by others using automated defibrillators may be more important to the patient's ultimate survival than is SCPR.

Recent animal research has shown that the potential is great for cerebral resuscitation.[14] Some proposed changes in SCPR techniques would appear to augment brain blood flow and coronary blood flow. Documentation of neurologic outcome, in addition to resuscitation and hospital discharge data, is necessary to evaluate the ultimate outcomes produced by standard SCPR and alternative techniques. Neurologic recovery after prolonged resuscitation is one promise that SCPR has never fulfilled.

THE PROCESS OF SCPR

It is important that both clinicians and basic researchers use precise language in describing their findings when studying the effectiveness of SCPR. If, for example, a researcher finds that standard closed-chest compressions are ineffective in generating coronary perfusion pressure in dogs, he must not generalize this finding to the entire process of SCPR in the clinical setting. SCPR as taught in the basic cardiac life support (BCLS) course denotes more than breathing and chest compressions.[1]

Recognition of Arrest

The American Heart Association and American Red Cross endeavor to teach the basics of the recognition of vital signs in their standard courses. Although evaluation of airway and breathing is relatively easy, determining the presence or absence of a pulse may be very difficult in the field, especially by a layman. The incidence of over-recognition and the performance of unnecessary chest compressions is unknown and should be studied.

Ventilation

A significant but unknown number of pure SCPR saves may be related to airway (A) and breathing (B) alone. Examples of such incidents are quick recoveries from near-drowning, lightning strikes, and drug overdoses, where ventilation alone may be enough to stabilize the patient until definitive care can be given. Since closed-chest massage was introduced in combination with rescue breathing, no randomized, controlled study of SCPR combination (airway, breathing, and closed compression — ABC) versus rescue breathing alone (airway and breathing — AB) has been done. Because there is concern about neurologic damage with low brain-blood-flow rates in the range of those generated by closed-chest compression, serious consideration should be given to a study to compare the AB-defibrillation protocol with the ABC-defibrillation protocol. (Based on current data and theory, the ethics of such a trial would be sound, but the legal complications of withholding chest compressions in the current litigious climate might be significant.)

System Notification

Teaching the public to contact the EMS system promptly has received some increased emphasis in BCLS classes. Milwaukee has a stable, civic-minded, and educated population, very similar to that of Seattle, and our citizens now contact the EMS paramedic system through the local fire departments. Specific access complaints are few, and virtually all cardiac arrest calls are handled with a "full assignment" of nearest engine, rescue squad, and paramedic unit. This tiered response system was designed from the Seattle model and has consistently produced EMT basic first response times of two to three minutes. Because virtually all calls and the corresponding dispatch can be completed in one minute, many victims of witnessed arrests receive their first SCPR from fire department EMTs within two to three minutes of the arrest. In such a rapid tiered response system, the effects of bystander SCPR may not produce measurable differences in outcome.

The Matter of Time

We have always been wary of and frustrated with estimates by citizens of down time for victims of cardiac arrest. At a cardiac arrest, a trained provider begins an almost-automated ABC sequence that has been honed by practice and testing.[11] It is, in the one-person mode, an almost all-encompassing activity requiring total concentration until help arrives. Nowhere in the teaching or testing of BCLS is the rescuer required to note the time of the arrest or the initiation of SCPR. Seldom in our system does the bystander actually note the time of arrest, and our postresuscitation interviews have not produced consistently reliable estimates. We think that citizen estimates of down time are highly suspect, and that other time comparisons made from those data carry the error forward. Such questionable data collection has been used by the Seattle group and others to generate, by statistical analysis, event time profiles that are said to give the best hospital admission and discharge outcomes.

To eliminate the uncertainty of time estimation from study data, we have defined the factor of resuscitation time[25] as a major component of total arrest time in our system. Resuscitation time, by our definition, is the time from paramedic arrival to the first sustained pulse and rhythm. In our system, the response time from notification of EMS until basic and paramedic unit arrival is documented by a data punch card system. Resuscitation time and response time thus are real numbers, not estimates. Study of resuscitation time confirms the intuitive reasoning that the shorter the time to successful defibrillation of VF (to a rhythm and a pulse), the better the prognosis. Further studies of the time parameters in cardiac resuscitation must be done.

FOCUS FOR FURTHER STUDY

Improvements in Chest Compression Technique

Considerable refinement in the understanding of the mechanism of blood flow with SCPR has occurred since the original proposal by Kouwenhoven et al.[26] The foundations for the systems of prehospital lay rescuers and EMS systems were developed in the late 1960s and early 1970s, before the discovery that the predominant mechanism of blood flow in SCPR is the "thoracic pump." In 1976, Criley et al[27] published their observation of "cough" SCPR, whereby vigorous coughing during cardiac arrest could produce near-normal arterial pressure. This observation soon was followed by other studies that refuted the cardiac compression theory of SCPR[28] blood flow. The discovery of jugular venous valves at the level of the thoracic inlet, which may create a low jugular pressure and facilitate brain blood flow, led to the concepts of "new" SCPR. By simultaneously providing ventilation and compressing the thorax (SCV-CPR), increased pressure gradients and improved carotid artery flow were generated. Since Criley's discovery, considerable experimental work has been done to find ways to improve cerebral and myocardial blood flow in SCPR.[28]

Several refinements of the original SCPR technique have been advocated as ways to improve cerebral and/or coronary artery blood flow. These are as follows: 1) SVC-CPR, simultaneous ventilation with chest compression;[29] 2) abdominal binding;[30,31] 3) volume loading;[31] 4) negative diastolic airway pressure;[32] and 5) IAC-CPR, interposed abdominal compression-CPR.[33-36]

Some techniques have been subject to limited clinical trials by other investigators.[31] Of the techniques proposed thus far, IAC-CPR seems to have the greatest potential for prehospital use, because it requires no equipment or basic technique change. Studies in canine models have shown substantial increases in cardiac output, diastolic arterial pressure, and diastolic arterial-venous pressure difference as compared to SCPR.[33,34] Berryman and Phillips evaluated the technique in a group of cardiac arrest patients after standard resuscitation was deemed unsuccessful.[35] Their results showed a 47% increase in mean arterial pressure, and a 39% increase in mean perfusion pressure during IAC-CPR.

We undertook a prospective, randomized study comparing IAC-CPR with SCPR for resuscitation of prehospital cardiopulmonary arrest victims, using the Milwaukee County Paramedic System.[35] After endotracheal intubation and initial quick-look defibrillation, the patients were assigned randomly to an IAC-CPR group, or to an SCPR group when they did not respond to the initial defibrillation. The total study group comprised 291 patients. The two experimental groups were compared for resuscitation rate (survival to hospital) and for frequency of emesis before and after intubation. The frequency of emesis was studied to determine whether abdominal compression increases the incidence of regurgitation. Of the 291 patients, 146 had SCPR and 45 (31%) were successfully resuscitated. Of the 145 patients treated with IAC-CPR, 40 (28%) were successfully resuscitated (P = NS). There was no statistically significant increase of emesis with IAC-CPR. We have completed the analysis of hospital discharge and neurologic recovery rates of the survivors, and we find no difference in outcome between the two techniques. Large-scale, randomized, prospective studies of any of the new SCPR techniques will be necessary before they may be accepted.

Open-Chest Cardiac Massage

Recent questions about the efficacy of standard SCPR have stimulated a new interest in research with open-chest SCPR (OC-CPR).[37] Experimentally OC-CPR generates higher arterial and lower venous pressures, and produces near-normal cardiac output and perfusion of both heart and brain.[37] In the laboratory, its superiority as a resuscitative technique is clear. Early clinical series reported up to a 28% survival-to-discharge rate, survival after two-and-one-half hours of OC-CPR, and successful resuscitation using OC-CPR after 75 minutes of SCPR had failed.[38] The technique is invasive, but has a remarkably low incidence of infection and iatrogenic injury. It must now be examined in direct comparison to SCPR. At least two randomized studies with human subjects are underway.

CONCLUSIONS

In the 25-year history of the practice of SCPR, there has been a heightened public awareness and the formation of organized prehospital systems that have had significant impact on communities. Early SCPR studies were not tightly controlled, but did generate some evidence for effectiveness of bystander SCPR and evidence to support the rapid delivery of definitive care. In some systems, the importance of the bystander initiating SCPR may have been overshadowed by the provision of a swift EMS response. Examin-

ing SCPR as a multifunctional process and analyzing the importance of each of its elements may be important in solving some of the apparent inconsistencies between studies. Large, randomized studies of SVC-CPR and OC-CPR in comparison to SCPR are needed.

A uniform reporting system for data, such as those proposed by Polnitsky[9] and Eisenberg et al,[10] must be widely applied. A reexamination of the original data by each study group and republication of the findings using a uniform reporting system format would be an important contribution to our understanding of the clinical application of SCPR. A national caucus to devise and disseminate a standard data format should be a priority for prehospital investigators.

REFERENCES

1. Cobb LA, Baum RS, Alvarez H, et al: Resuscitation from out-of-hospital ventricular fibrillation: Four year follow-up. *Circulation* 1975;51,52(Suppl 3):223-228.

2. Eisenberg MS, Bergner L, Hallstrom A: Cardiac resuscitation in the community: Importance of rapid provision and implications for program planning. *JAMA* 1979;241:1905-1907.

3. Thompson RG, Hallstrom AP, Cobb LA: Bystander-initiated cardiopulmonary resuscitation in the management of ventricular fibrillation. *Ann Intern Med* 1979;90:737-740.

4. Diamond NJ, Schofferman J, Elliot JW: Factors in successful resuscitation by paramedics. *JACEP* 1977;6:42-46.

5. Eliastam M, Duralde T, Martinez B, et al: Cardiac arrest in the emergency medical service system: Guidelines for resuscitation. *JACEP* 1977;6:525-529.

6. Lauterbach SA, Spadafora M, Levy R: Evaluation of cardiac arrests managed by paramedics. *JACEP* 1978;7:355-357.

7. Liberthson RR, Nagel EL, Hirschman JC, et al: Prehospital ventricular defibrillation: Prognosis and follow-up course. *N Engl J Med* 1974;291:317-321.

8. Amey BD, Harrison E, Staub E: Sudden cardiac death: A retrospective and prospective study. *JACEP* 1976;5:429-433.

9. Polnitsky CA, Capone RJ, Gagnen MT, et al: Prehospital coronary care: Proposal for a uniform reporting system. *JAMA* 1977;237:134-139.

10. Eisenberg MS, Bergner L, Hearne T: Out of hospital cardiac arrest: A review of major studies and a proposed uniform report system. *Am J Pub Health* 1980;70:236-240.

11. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). *JAMA* 1980;244:483-493.

12. Eisenberg MS, Copass MK, Hallstrom A, et al: Management of out of hospital cardiac arrest: Failure of basic EMT services. *JAMA* 1980;243:1049-1051.

13. Enns J, Tweed WA, Donen MB: Prehospital cardiac rhythm deterioration in a system providing only basic life support. *Ann Emerg Med* 1983;12:478-481.

14. Eisenberg MS, Bergner L, Hallstrom A: Paramedic programs and out-of-hospital cardiac arrest. I. Factors associated with successful resuscitation. *Am J Pub Health* 1979;69:30-38.

15. Kowalski R, Thompson BM, Horwitz L, et al: Bystander CPR in prehospital coarse ventricular fibrillation. *Ann Emerg Med* 1984;13:1016-1020.

16. Stueven HA, Mateer J, Thompson B, et al: Bystander first responder CPR: Ten years experience in a paramedic system, abstract. *Ann Emerg Med* 1985;14:510.

17. Longstreth W, Inui T, Cobb LA, et al: Neurologic recovery after out of hospital cardiac arrest. *Ann Intern Med* 1983;98(Part 1):588-592.

18. Ornato J, Gonzales E, Morkunas A, et al: Delayed paramedic response time as the principal cause of acidosis in out-of-hospital cardiac arrest, abstract. *Am J Emerg Med* 1984;2:356-357.

19. Roth R, Stewart RO, Rogers K, et al: Out-of-hospital cardiac arrests: Factors associated with survival. *Ann Emerg Med* 1984;13:237-243.

20. Aprahamian C, Thompson B, Mateer J, et al: Factors in sudden cardiac death decision making, abstract. *Ann Emerg Med* 1985;14:510.

21. Cummins RO, Eisenberg M, Hallstrom A: The survival benefit of early CPR for out of hospital arrest, abstract. *Am J Emerg Med* 1984;12:349.

22. Eisenberg MS, Copass MK, Hallstrom AP, et al: Treatment of out-of-hospital cardiac arrests with rapid defibrillation by emergency medical technicians. *N Engl J Med* 1980;302:1379-1383.

23. Stults KR, Brown DD, Schug VL, et al: Prehospital defibrillation performed by emergency medical technicians in rural communities. *N Engl J Med* 1984;310:219-223.

24. Safar P: Cerebral resuscitation after cardiac arrest. Summaries and suggestions. *Am J Emerg Med* 1983;2:198-214.

25. Pionkowski R, Thompson BM, Aprahamian C: Resuscitation time in ventricular fibrillation — A prognostic indicator. *Ann Emerg Med* 1983;12:733-738.

26. Kouwenhoven WB, Jude JR, Knickerbocker GG: Closed-chest cardiac massage. *JAMA* 1960;173:1064-1067.

27. Criley J, Blaufuss A, Kissel G: Cough induced cardiac compression — Self-administered form of cardiopulmonary resuscitation. *JAMA* 1976;236:1240-1250.

28. Criley J, Niemann J, Rosborough J: Cardiopulmonary resuscitation research 1960-1984: Discoveries and advances. *Ann Emerg Med* 1984;13(Part 2):756-758.

29. Chandra N, Tsitlik J, Weisfeldt M, et al: Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressures simultaneous with chest compression. *Am J Cardiol* 1981;98:1053-1056.

30. Redding J: Abdominal compression in cardiopulmonary resuscitation. *Anesth Analg* 1971;50:668.

31. Mahoney BD, Mirick MJ: Efficacy of pneumatic trousers in refractory prehospital cardiopulmonary arrest. *Ann Emerg Med* 1983;12:8-12.

32. Weisfeldt M, Chandra M: Physiology of cardiopulmonary resuscitation. *Ann Rev Med* 1981;32:435.

33. Ralston SH, Babbs CF, Niebauer MS: Cardiopulmonary resuscitation with interposed abdominal compression in dogs. *Anesth Anagl* 1982;61:645-651.

34. Voorhees WD, Niebauer MJ, Babbs CF: Improved oxygen delivery during cardiopulmonary resuscitation with interposed abdominal compressions. *Ann Emerg Med* 1983;12:128-135.

35. Berryman CR, Phillips GM: Interposed abdominal compression-CPR in human subjects. *Ann Emerg Med* 1984;13:226-229.

36. Mateer JR, Stueven HA, Thompson BM, et al: Prehospital IAC-CPR versus standard CPR: Paramedic resuscitation of cardiac arrests. *Am J Emerg Med* 1985;3:143-146.

37. Bircher N, Safar P: Manual open chest cardiopulmonary resuscitation. *Ann Emerg Med* 1984;13(Part 2):770-772.

38. Del Guercio LRM, Feins NR, Cohn JD, et al: A comparison of blood flow during external and internal cardiac massage in man. *Circulation* 1965;32(Suppl II):171-180.

"Champagne tastes on a beer budget?"

Try Acme Disposable Instrument Trays

ONE TIME® combines economy with class

Reusable quality at disposable prices? But of course! With One Time, you'll cut costs without cutting performance. Scissors. Scalpels. Forceps. Hemostats. Needle holders. All are custom forged, precision-ground instruments of nickel-plated steel manufactured in the U.S.A.

And fortunately, all are at your disposal in the largest selection of procedure trays available. From Wound Closure to General Purpose... we have prepackaged trays with the appropriate instruments and supplies to match your procedures. We can also customize special trays for specific needs. Whichever you choose, both offer dramatic savings over hospital-prepared trays.

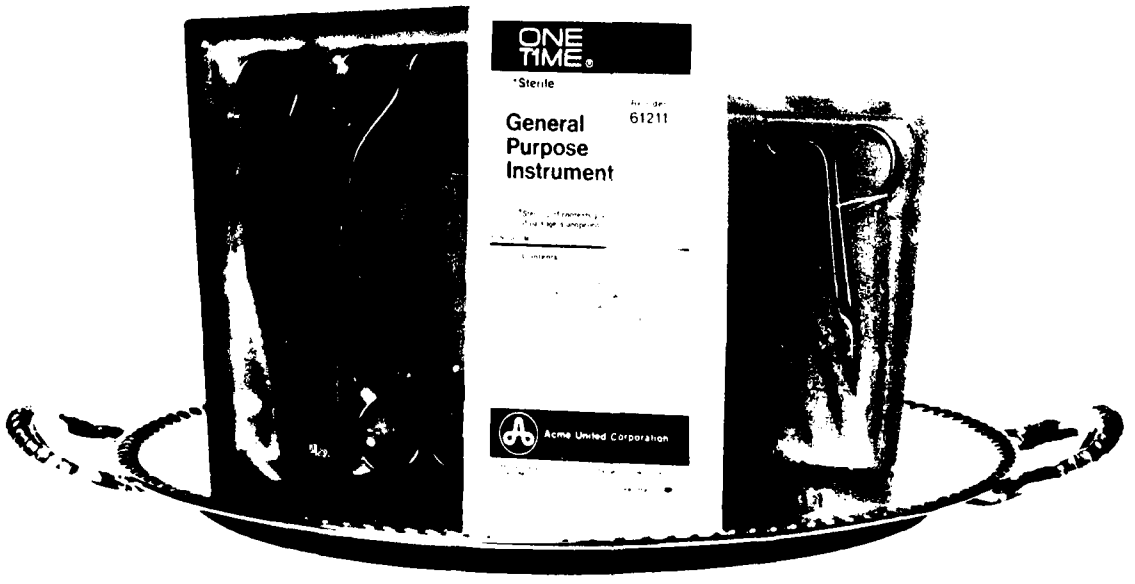
In fact, Acme has been instrumental in saving money in many hospitals. Consider these documented examples*:

- Utilizing the General Purpose Tray only, a 750-bed Boston, Massachusetts, hospital figured a savings of $5.41 per tray or $23,371.20 per year. (Based on a reported usage of 4,320 trays annually.)
- A 201-bed hospital in Chicago, Illinois, using just the Wound Closure Tray can save $8.93 per tray or $3,000.48 annually. (Based on a reported usage of 336 trays per year.)

As you can see, One Time really does combine economy with class. And Acme would be delighted to prove it with a FREE demonstration and cost evaluation for your department. Simply contact us at:

1-800-TEL-ACME
(1-800-835-2263)

Acme has the most complete line of standard disposable trays and instruments available. We can also customize special trays for special needs.



Acme makes disposable trays
Socially Acceptable

Acme United Corporation
Medical Products Division
Fairfield, Connecticut 06430

*Data on file at Acme United Corporation

Changing the way the world heals™

Bruce A. Flashner, M.D.
with partners and associates of
The Flashner Medical Partnership

presents a unique concept in seminars that takes you from the first step to the very top!

Seminar will be held:
September 21st 9 a.m. - 5 p.m.
September 22nd 9 a.m. - 4 p.m.

Catch the concept before the concept catches you (or your patients)!

Convenient Extended Hour Care Center Seminar

INSIGHT—*"Thorough, practical, well-planned, well-paced, easily digested, easily applied, full of "pearls," timely, information not available elsewhere."* G.P., M.D., Boston, MA

On Saturday, September 21st and Sunday, September 22nd you could accumulate enough knowledge to successfully OPEN, OPERATE and PROFIT in your own free-standing immediate care center practice or expand the practice you are currently operating. This will be a DETAILED OPERATIONALLY ORIENTED presentation developed for physicians, managers, entreprenuers, and hospital administrators. Clear, concise details that will show you how to join in on this growing industry with as little as $10,000 of your own capital.

INFORMATION—*"Comprehensive, straight forward information that anyone considering such an endeavor shouldn't be without!"* M.S., Florence, S.C.

This unique seminar will literally walk you through

DEVELOPMENT EQUIPMENT AND SUPPLY NEEDS FINANCING OWNERSHIP MEDICAL ORGANIZATION LEGAL AND REGULATORY ISSUES STAFFING PATIENT FLOW WORKER'S COMPENSATION OPERATIONS ACCOUNTING BILLING RECEIVABLES MARKETING AND ADVERTISING COMPUTERS

INSTRUCTION—*"Very practical and 'nuts and bolts' type information which will help me greatly when I open my center."* W.M., M.D., Milford, MA

No seminar has ever been able to offer so much...because no single group has acquired so much hands on experience. Recently, The Flashner Medical Partnership sold 22 of The Doctors Officenters to Humana, Inc. FMP continues however, to provide the medical services at 22 Chicago area offices. At the same time, the partnership totally owns and operates 9 centers in the New York market areas. Dr. Flashner, along with his partners and management associates are among the leading recognized experts in their areas of expertise.

TWO-DAY SEMINAR REGISTRATION—The fee for this seminar is $1000. For each additional attendee from the same organization the fee is $850. For those individuals whose registration is post marked before September 6th, save $50 on each attendee. The fee includes all workbook materials, seminar instruction, refreshment breaks and lunches. The seminar will be held at the Marriott O'Hare Hotel 8535 W. Higgins Road, Chicago, Illinois 60631 (312) 693-4444 conveniently located near O'Hare airport. The entire fee is refundable if cancellation notice is received in our office by September 6, 1985. Airline and Hotel Room Reservations may be made through Travel Duet, Inc. by calling toll free 1-800-323-1276 (please refer to The Flashner Medical Partnership seminar). As an added bonus to seminar participants Travel Duet has arranged for a 35% discount for all travelers flying United Airlines.

The Flashner Medical Partnership

312-433-6411 or 1-800-633-2373

REGISTRATION FORM
The Convenient Extended Hour Physician's Office Seminar

☐ Please reserve _____ registrations for your two-day program

Registrants (please print)

☐ Check enclosed for $ _____ Payable to The Flashner Medical Partnership

☐ Mastercard ☐ Visa Account Number _____

Signature _____

NAME _____ TITLE _____

Organization _____ Address _____

City _____ State _____ Zip _____ Telephone _____

NAME _____ TITLE _____

Organization _____ Address _____

City _____ State _____ Zip _____ Telephone _____

MCM 123

Send to: The Flashner Medical Partnership
Attn: Deborah Gold 477 Roger Williams Ave. Highland Park, IL 60035

SPECIAL CONTRIBUTION
computers, CPR, defibrillator, resuscitation

Automatic External Defibrillators: Clinical, Training, Psychological, and Public Health Issues

Automatic external defibrillators (AEDs) will be used by spouses, family members, emergency first-responders, and the citizenry at large. Such use, however, raises a number of clinical, training, psychological, and public health issues. Clinical issues: Is cardiac arrest to be verified by the operator or the AED? Second verification systems, such as breath detectors, produce errors of omission, but greatly expand the pool of potential users. The relative merits of high sensitivity and low specificity in arrest verification must be defined by clinicians relative to the setting and the potential users. AEDs require cessation of basic CPR during their assessment periods; clinicians must determine the tradeoff between long interruption of basic life support and much earlier delivery of countershocks. Training issues: Criteria for those to be trained include consideration of who the patient will be and who the AED operator might be. AEDs pose a familiar adult education problem, that is, acquisition of a new psychomotor skill and retention of that skill for long periods before performance. What are the best teaching techniques? Currently available AEDs have different designs for device-operator interaction. Which design is most likely to assure proper performance during an actual arrest? Psychological issues: What are the psychological effects of learning about, living with, and eventually using an AED? The development of the automatic external defibrillator constitutes the most recent attempt to achieve early defibrillation of patients in cardiac arrest. The potential public health effect of such devices is enormous. [Cummins RO, Eisenberg MS, Moore JE, Hearne TR, Andresen E, Wendt R, Litwin PE, Graves JR, Hallstrom AP, Pierce J: Automatic external defibrillators: Clinical, training, psychological, and public health issues. Ann Emerg Med August 1985;14:755-760.]

Richard O Cummins, MD, MPH, MSc
Mickey S Eisenberg, MD, PhD
James E Moore, PhD
Thomas R Hearne, PhD
Elena Andresen, MA
Rosalie Wendt, RN
Paul E Litwin, MS
Judith R Graves, RN, MS
Alfred P Hallstrom, PhD
Judith Pierce, MA
Seattle, Washington

From the King County Emergency Medical Services Division and the Departments of Medicine, Psychiatry, and Biostatistics, University of Washington, Seattle, Washington

Presented at the 1985 UAEM/RIEM Research Symposium in Orlando, Florida, February 7-8, 1985.

Supported in part by grants from the National Center for Health Services Research (HS-05174, HS-04894), the Cardiac Resuscitator Corporation, Wilsonville, Oregon, the Physio-Control Corporation, Redmond, Washington, and the Laerdal Foundation, Stavanger, Norway.

Address for reprints: Richard O Cummins, MD, Room 508, Smith Tower, 506 Second Avenue, Seattle, Washington 98104

INTRODUCTION

Who's Got the Joules?

Early defibrillation alone can improve the survival of patients who collapse in ventricular fibrillation (VF).[1,2] For decades, the care of out-of-hospital cardiac arrest patients has focused on who carries the defibrillator and performs the defibrillation.[3] First, defibrillators were brought to the patient by physicians in mobile coronary care units.[4] Then highly trained, nonphysician personnel (paramedics) were shown to substitute adequately for physicians.[5] More recently, less skilled emergency personnel, emergency medical technicians (EMTs), have been trained to defibrillate patients, and their effectiveness has been confirmed in several controlled evaluations.[1,2] Each successive transfer of defibrillator operation has been an effort to get the defibrillator to the collapsed patient more quickly.

The ultimate extension of these efforts to achieve earlier defibrillation has been to give the defibrillator to the patient, in the form of automatic implantable defibrillators,[6] or to family members and coworkers, in the form of automatic or semi-automatic external defibrillators.[7,8] In theory, the public health impact of such devices (in particular the automatic external defibrillator) will be enormous.[9] The potential widespread use of automatic external defibrillators by spouses, family members, emergency first responders, and the citizenry at large raises a number of clinical, training, public health, and psychological issues which are presented here. The discussion is based on our experience with automatic external defibrillators used in

the home and by minimally trained emergency personnel.[3]

TYPES OF DEFIBRILLATORS

By 1985, four general types of defibrillators were available for use in the prehospital setting. From the perspective of "who's got the joules," each type involves different issues.

Blind Defibrillators

Defibrillators are sold with no means of rhythm identification. Although these defibrillators are usually meant to be components of a larger system that includes a monitor, the device is available separately. No operator knowledge of cardiac rhythms is necessary or even useful with such devices. This defibrillator may be attached quickly to a patient in cardiac arrest, and a countershock may be delivered. Because ventricular fibrillation is the most common initial rhythm in cardiac arrest, there is a certain rationale for such devices. Blind defibrillators are sold almost exclusively to dental professionals, who have an extremely small expectation of caring for patients in cardiac arrest, but who have some legal responsibility to provide emergency care should an arrest occur.

Standard Manual Defibrillators

Standard manual defibrillators provide the operator with some method for visual identification of the cardiac rhythm. These devices require maximum operator knowledge and skill. Training in rhythm recognition and proper operation of the manual defibrillator can be accomplished in a 10- to 12-hour course for most emergency medical paraprofessionals.[1,2,9] Operation of a manual defibrillator requires frequent practice, refresher training, and field experience.

Semiautomatic External Defibrillators

Semiautomatic external defibrillators have two adhesive electrodes that are easily attached to the chest of a person in cardiac arrest. Messages on a liquid crystal display screen guide the operator through verification of cardiac arrest, and tell the operator not to touch the patient while the rhythm is automatically assessed. If VF is present, the device "advises a shock" and cues the operator to press a "shock" button. The device delivers the countershock through the adhesive electrodes. Most lay people can learn to operate these defibrillators. Rhythm identification by the operator is not necessary, but these devices do require an important operator decision and action (to push the "shock control" switch if a shock is "advised").

Fully Automatic External Defibrillators

As do semiautomatic defibrillators, these sense cardiac rhythm through two adhesive pads attached to the chest (some models have one of the two electrodes incorporated in an oral airway). The operator must attach the device properly and press the power ON switch. Once attached and placed in automatic mode, these defibrillators analyze the surface ECG signal and automatically charge and deliver countershocks if ventricular fibrillation is present. No further operator actions are required. These defibrillators require minimum operator knowledge and skill: no operator decisions are necessary beyond attaching the device to a patient and turning on the power.

ISSUES RAISED BY AEDs

Verification of Cardiac Arrest

There is concern among people involved with the development of AEDs about whether AEDs will be used only by individuals trained to diagnose a cardiac arrest (that is, trained to recognize an unconscious, pulseless, and breathless individual), or whether the devices will occasionally be used by unskilled, minimally trained individuals. Inadequate assessment of the need for ventilation and compression has been reported frequently in studies examining skill retention in CPR trainees. An unsophisticated, inexperienced operator may confuse a number of conditions — syncope, alcohol or drug intoxication, seizures, or shock — with cardiac arrest. In these and other situations, surface signal noise from patient movements, loose leads, environmental sources, or even perfusing rhythms with unusual characteristics could fool a VF detector depending on the surface ECG. A potentially lethal countershock could be delivered.

One is led to the question of whether AEDs must be manufactured with a system for verification of cardiac arrest independent of the surface ECG, or whether the assumption can be made that operators of the device will attach it only to people in full cardiac arrest. Currently available AEDs possess second verification systems. One device has an optional breath detector incorporated into an oral electrode to assure that respirations have ceased. This oral electrode also stimulates the gag reflex, thus acting as an additional indicator that blood flow to the midbrain has ceased. The AED of another manufacturer measures impedance between its two sternal/apex adhesive electrodes as a method to detect chest wall respiratory movements. Both products send high-frequency impedance signals between the electrodes to detect loose leads.

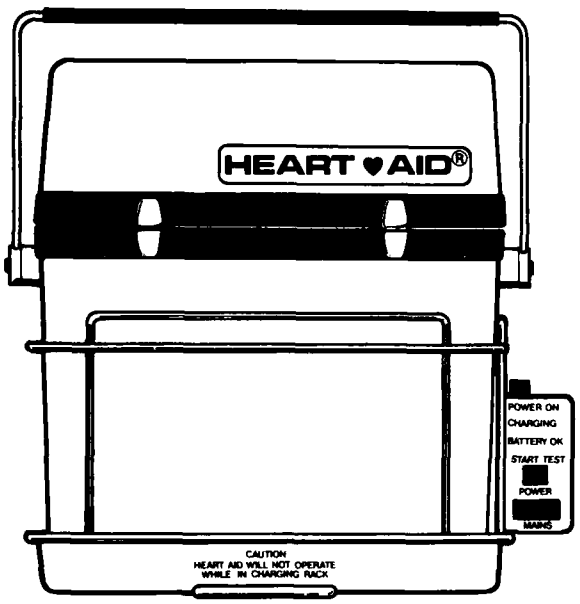
Fig. *Step-by-step guide to the use of the automatic external defibrillator. This demonstrates the relative complexity of integrating basic cardiopulmonary resuscitation with the attachment and operation of the AED. (Developed by and used with the permission of the King County Emergency Medical Services Division.)*

The understandable concern to make the devices as safe as possible in all circumstances may result in safe but relatively ineffective products. When placed in the home, the workplace, and by first-responders, AEDs will frequently be attached to cardiac arrest patients within one to two minutes of the collapse. Many of these patients, even though they may be in VF, may still have agonal respirations, seizures, or other body movements. If a second verification system requires complete absence of respiratory and other movement before delivery of a countershock, the advantages of early defibrillation are lost.[8,10] In the hands of trained EMS personnel, a second verification system is unnecessary and, in fact, has prevented rhythm assessment and shock delivery in several patients.[11]

The Sensitivity/Specificity Issue

How sensitive must an AED be? Is there a dividing line between asystole, a rhythm that perhaps need not be shocked, and ventricular fibrillation, which should be? Of the AEDs currently available, one device requires a signal amplitude of ≥ 1.5 mm (150 microvolts), and another requires ≥ 2.0 mm (200 microvolts). Clinicians would not accept failure to shock a patient whose VF is almost 2.0 mm

HEART AID GUIDE



HEART♥AID® GUIDE

1 

ASSESS ABC's

AIRWAY OPEN

BREATHING?
LOOK, LISTEN & FEEL

CHECK PULSE

2 

CALL EMS
- ADDRESS
- CPR IN PROGRESS

BRING H.A. TO PATIENT

3 

CPR ONE CYCLE

2 BREATHS 15 COMPRESSIONS

4 

CONNECT HEART AID

5 HEART AID

ON

COUNT TO 15

TURN ON
STAND BACK
WHEN VOICE STOPS
COUNT TO 15

6 HEART AID

OFF

TURN OFF

7 

CHECK PULSE

IF PULSE MONITOR BREATHING

IF NO PULSE

CPR ONE CYCLE

8 

REPEAT 5-8
UP TO 3X THEN
CONTINUE CPR
UNTIL HELP
TAKES OVER.

2 BREATHS 15 COMPRESSIONS

high. The difficulty is that a device that is sensitive to very fine VF will probably have lower specificity, and may misdiagnose signal noise as VF. Furthermore, optimal sensitivity/specificity may vary, depending on the clinical setting and the operator. When used by trained and experienced EMS personnel, and AED may have high sensitivity and low specificity, because the operators are able to verify cardiac arrest and react to and minimize signal noise. In settings in which early defibrillatory capability never existed in the home or in remote or rural areas, an AED with only modest sensitivity may represent a marked improvement. Because the operator in these settings will have had little experience with cardiac arrests, low sensitivity with high specificity may be preferred.

Algorithm programs for the detection of cardiac rhythms by AEDs identify VF through analysis of different features or different combinations of features of the ECG signal. These include amplitude, frequency, wave form morphology,[13] power spectrum density,[14] time domain technique,[15] and time away from the isoelectric line.[6] When a patient's rhythm meets the device's criteria for VF, the device will deliver a countershock. The advantage of AEDs is that the criteria for VF (depending on the setting, the operator, and the local standard of care) can be changed by the manufacturer. Clinicians using the results of field trials must help define these criteria.

The "Stop CPR" Issue

An AED requires a minimum amount of time to assess cardiac rhythm, to charge its capacitors, and to deliver the countershock. Basic life support in the form of CPR must cease during this period. Although AHA standards are that basic CPR should not be interrupted for more than five seconds, currently available AEDs require that CPR stop for at least 10 to 15 seconds. An attempt to sequence countershocks would require even longer interruptions. What is the tradeoff between long interruptions of basic life support and the much earlier delivery of countershocks? Data from many studies confirm the necessity of early countershocks: CPR does not defibrillate people, electricity does.[1,5,16] Nevertheless, there is strong resistance from some clinicians and EMS personnel to the requirement for relatively long interruptions of CPR. These attitudes, plus misconceptions such as the idea that defibrillation should be delayed while CPR is administered to "prime" VF for easier conversion, may inhibit wide acceptance of AEDs.

Who Should Be Trained?

An AED requires two people: the patient who has experienced a cardiac arrest and may need defibrillation, and the operator who must recognize the cardiac arrest and properly attach the AED. Depending on the setting, finding the suitable combination of patient and operator can be complicated. For example, there are many patients at high risk for lethal arrhythmias who theoretically would be prime candidates for home placement of an AED. Many of these patients, however, may not be appropriate candidates. This group may include many permanently disabled patients in extended care facilities. Clinicians and family members must decide on the propriety of placement of an AED, depending on the clinical condition of the patient and individual preferences.

Patients who are excellent candidates for AED placement at home may lack an operator who will be available readily, thus having a high likelihood of witnessing the arrest. In our experience, we have often decided not to place an AED because a patient lived entirely alone, or was left alone much of the day when family members attended to their other responsibilities. Patients who have returned to work after a cardiac arrest have faced the problems of having to carry the AED to work, and of obtaining AED training for their coworkers and other non-household members. Similarly we have been unable to designate an appropriate AED operator in some cases because of the physical disabilities, intellectual limitations, or incompatible attitudes of the potential operator.

Skill Acquisition and Retention Issues

Because of the demonstrated[1,5,16] benefit of early-bystander-initiated CPR and because of AHA standards,[17] one-person CPR training has been integrated into AED protocols. The skill of using an AED is, in large part, the skill of basic CPR. For the operator, learning to use an AED in combination with basic CPR poses a familiar problem in adult education — that of acquiring a new psychomotor skill during initial training, and then retaining that skill for weeks or months before finally being called on to perform.

To teach AED operation, we have used a highly individualized, multimedia approach including verbal explanation, visual aids, observed demonstrations, participatory demonstrations, role-playing, and coaching. Every operator is trained until he performs the AED arrest protocol to meet predetermined criteria.

A number of studies have demonstrated a marked deterioration over time in the psychomotor skills of CPR.[10,20-23] Our experience confirms these observations. To address the problem of skill retention, our research team revisits each patient and his AED operator(s) at intervals of six weeks, three months, six months, and one year after initial training. The AED operator is retested at these visits and, if performance is weak, he is retrained to meet criteria. Several methods of enhancing skill retention are used, including homework assignments to practice using the AED, and telephone reminders.

The central question in skill acquisition and retention is whether family members will operate the AED properly during an actual cardiac arrest. At the time of a cardiac arrest, the AED operator must remember and perform an ordered sequence of actions (Figure). These acts must be remembered and performed during an intensely dramatic and emotion-filled moment, that of the sudden death of a close companion or family member. It is too soon to draw conclusions about how the AED operator will perform at these moments. Only two patients enrolled in the AED study group have suffered a cardiac arrest. Neither operator performed the protocol flawlessly, and one operator erred in a way that would have prevented a countershock of ventricular fibrillation by the AED (that patient was not in VF).

Device-Operator Interaction

Given the complexity of actually using an AED at the time of a cardiac arrest, there is a question concerning the best design for interaction between the operator and the device. The manufacturers of the two currently available AEDs have taken

somewhat different approaches. One device requires the operator to memorize a sequence of steps and possible patient responses (Figure). A voice synthesizer provides verbal cues for stopping CPR, checking loose electrodes, and avoiding contact with the patient during capacitor charge and countershock.

With the other device, the operator is led through a sequence of steps in an interactive fashion, with the operator indicating when each step has been completed by pushing YES/NO control switches. The operator also must push a button to deliver an indicated shock. The sequencing of steps and the occurrence of errors are shown on a liquid crystal display that the operator must read. Both devices supply additional information to the user by alarm tones and, in the case of the fully automatic defibrillator, light signals.

Which of the two approaches (memorization of the protocol sequence, or sequenced visual prompts that give step-by-step guidance to the operator) is more effective is questionable. At present we think successful use of an AED is more dependent on overall training than on the details of device-operator interaction. If the operator makes appropriate initial responses, including initiation of CPR, activation of the emergency medical system, retrieval of the AED, and attachment of the device to the patient, we think appropriate response to the AED's signals should be forthcoming. High-quality training and frequent practice should permit either device to be used effectively.

We have learned that the most difficult aspect of the AED protocols is not pushing the switches on the device, but interposing the steps of basic CPR with retrieving and operating the AED. One way to simplify training and actual use of the device would be to eliminate a prescribed period of initial CPR, and to eliminate interposed CPR between AED assessment and treatment cycles. This would simplify greatly the protocol sequence, increase the probability of correct AED operation, and shorten the time to shock administration. CPR would be started immediately after a rapid series of shocks if the patient had not regained a palpable pulse. As clinical experience is gained with AEDs, we may learn that to assure a high frequency of satisfactory attachment and operation, prior and interposed CPR cycles may have to be eliminated for minimally trained lay responders.

Psychological Issues

By definition, candidates for home placement of an AED are at high risk for sudden cardiac arrest. In our study, we have enrolled only those patients who have recently experienced an out-of-hospital cardiac arrest. The period following such an event is a time of major psychological adjustment. It is not known how learning about and living with an AED in this period will affect patients and their families. We have been evaluating the psychological and behavioral effects of cardiac arrest in patients and their families, the changes in adjustment over time following an arrest, and the psychological and behavioral effects of AED training and home placement. Our results thus far suggest that home placement of an AED imposes no significant detrimental effects, either psychological or behavioral, when compared to training in CPR alone (JE Moore, et al, unpublished data). Indeed, our results indicate that patients are better adjusted psychologically after their spouses have been trained either in AED use and CPR or CPR only.

Patients and family members in our study have expressed generally positive attitudes toward training in CPR and use of an AED. In the homes of two patients, however, conspicuous display of the AED caused distress, so much so that the location of the device (recommended to be placed near the telephone) was changed. Family members cite a sense of security that comes from having such a device, and a fulfillment of their needs to be able to "do something" should the patient have a cardiac arrest. Chadda and Kammerer have observed similar positive attitudes in their study of home defibrillation and CPR training.[3] When clinical uses of the AEDs occur, we will assess positive outcomes, such as a sense of accomplishment that something was attempted, and negative outcomes, such as guilt from failure to use the device correctly.

In our study, we have observed a tendency in both patients and spouses to deny the patient's increased health risk, and to attempt to reduce psychological stress for the patient. Through these mechanisms of denial and avoidance of stress, our patients appear in general to have experienced only mild psychological disturbances, disturbances that largely have disappeared within three months of the original cardiac event. Denial can be a useful mechanism for facilitating adjustment, as well as for increasing survival for cardiac patients. We suspect, however, that this occurrence of denial may constitute a future barrier to home placement of AEDs. Patients and family members who perceive little or no vulnerability to a future cardiac arrest are unlikely to accept such a device, especially if it represents major time and financial costs.

We have encountered other psychological barriers to acceptance of AEDs in the home. In addition to an occasional lack of medical sophistication and understanding, these is also a general fear of any unfamiliar and somewhat mysterious medical technology. For the operator, using an AED may represent a distasteful and invasive medical act. For older adults, training in the use of an AED requires acquisition of new and intimidating psychomotor skills. During our recruitment interviews, we have encountered an understandable reluctance on the part of some family members to accept responsibility for appropriate action at some future cardiac arrest. In addition, occasionally patients and family members will refuse to accept the concept of resuscitation, citing religious or moral reasons.

Public Health Issues

The availability of AEDs raises many public health issues. Currently the devices are prescription items, to be purchased and used only under the direction of licensed physicians. Will this arrangement continue in the future? Who will pay for AEDs prescribed for home use? Will AEDs be covered by third-party reimbursement plans? What will be the exact indications and contraindications used by physicians?

In addition to patients and family members, AEDs can be used by many groups of lay responders. Which lay responders? How will there be medical control of the dissemination of AEDs in the community at large? These and other issues must be addressed in the future.

CONCLUSION

Automatic external defibrillation is

a technology that may have a major impact on survival from out-of-hospital cardiac arrest. Criteria for selection of patients and the best methods of training both operators and lay responders are now being identified, as well as the psychological effects of learning about, living with, and using AEDs. As this technology is developed and applied clinically, we are gaining a greater understanding of not only its potential, but also the many clinical, psychological, and public health issues that it raises.

The authors wish to thank Marlys VanBeeck, Douglas Austin, and Rebecca Hanley of the King County Emergency Medical Services Division, who provided research assistance and organizational support; Bruce Haggar and John Kuphal of the Cardiac Resuscitator Corporation, and Carl Morgan of the Physio-Control Corporation, who provided technical advice; Douglas Stewart, MD, Robert Haynes, MD, Gerald Lorch, MD, and J Patrick Reagan, MD, who provided medical review as members of our King County Medical Advisory Committee; and a number of citizens of King County who graciously agreed to participate in these studies.

REFERENCES

1. Eisenberg MS, Copass MK, Hallstrom AP, et al: Treatment of out-of-hospital cardiac arrests with rapid defibrillation by emergency medical technicians. *N Engl J Med* 1980;302:1379-1383.

2. Stults KR, Brown DD, Schug VL, et al: Prehospital defibrillation performed by emergency medical technicians in rural communities. *N Engl J Med* 1984; 310:219-223.

3. Cummins RO, Eisenberg MS: Automatic external defibrillation: Evaluations of its role in the home and in emergency medical systems. *Ann Emerg Med* 1984; 13(Part 2):798-801.

4. Pantridge JF, Geddes JS: A mobile intensive care unit in the management of myocardial infarction. *Lancet* 1967;2: 271-273.

5. Eisenberg MS, Bergner L, Hallstrom AP: Out-of-hospital cardiac arrest: Improved survival with paramedic services. *Lancet* 1980;1:812-815.

6. Mirowski M, Reid PR, Winkle RA, et al: Mortality in patients with implanted automatic defibrillators. *Ann Intern Med* 1983;98(Part 1):585-588.

7. Cummins RO: Options to provide earlier definitive care, in Eisenberg MS, Bergner L, Hallstrom AP (eds): *Sudden Cardiac Death in the Community.* Philadelphia, Praeger Scientific, 1984, pp 87-100.

8. Hallstrom A, Eisenberg M, Bergner L: The potential use of automatic defibrillators in the home for management of cardiac arrest. *Med Care* 1984; 22:1083-1087.

9. Copass MK, Eisenberg MS, Damon SK: *EMT Defibrillation.* Westport, Connecticut, Emergency Training, 1984.

10. Martin WJ, Loomis JH, Lloyd CW: CPR skills: Achievement and retention under stringent and relaxed criteria. *Am J Public Health* 1983;73:1310-1312.

11. Weaver WD, Ray R, Hallstrom AP, et al: Improving survival from out-of-hospital cardiac arrest: The potential benefit of automatic external defibrillators. *Am J Emerg Med* 1984;2:362A.

12. Cummins RO, Eisenberg MS, Bergner L, et al: Sensitivity, accuracy and safety of an automatic external defibrillator: Report of a field evaluation. *Lancet* 1984;2:318-320.

13. Aronson AL, Haggar B: The automatic defibrillator-pacemaker: Clinical rationale and engineering design. *Medical Instrum* 1985, In press.

14. Forster FK, Weaver WD: Automatic recognition of ventricular fibrillation and other rhythms in patients developing cardiac arrest, in *IEEE Computer Society — 1983 Computers in Cardiology.* Los Angeles, IEEE Computer Society, 1983, pp 245-248.

15. Kuo S, Dillman R: Computer detection of ventricular fibrillation, in, *IEEE Computer Society — 1980 Computers in Cardiology.* Los Angeles, IEEE Computer Society, 1980, pp 347-349.

16. Eisenberg MS, Bergner L, Hallstrom A. Paramedic programs and out-of-hospital cardiac arrest: I. Factors associated with successful resuscitation. *Am J Public Health* 1979;69:30-38.

17. Cummins RO, Eisenberg MS, Hallstrom AP, et al: Survival of out-of-hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. *Am J Emerg Med* 1985;3:114-118.

18. Cummins RO, Eisenberg MS: Prehospital cardiopulmonary resuscitation: Is it effective? *JAMA* 1985;253:2408-2412.

19. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). *JAMA* 1980; 244(suppl):453-509.

20. Winchell SW, Safar P: Teaching and testing lay and paramedic personnel in cardiopulmonary resuscitation. *Anesth Analg Curr Res* 1966;45:441-449.

21. Weaver FJ, Ramirez AG, Dorfmann SB, et al: Trainees' retention of cardiopulmonary resuscitation. How quickly they forget. *JAMA* 1979;241:901-903.

22. Gombeski WR, Effron DM, Ramirez AG, et al: Impact on retention: Comparison of two CPR programs. *Am J Public Health* 1982;72:849-852.

23. Wilson E, Brooks B, Tweed WA: CPR skills retention of lay basic rescuers. *Ann Emerg Med* 1983;12:482-484.

24. Chadda K, Kammerer R: Patient and family acceptance of home defibrillation and CPR program, abstract. *Circulation* 1984;70(suppl II):463.

THE DURICEF®
(CEFADROXIL) CAPSULES, 500 mg TABLETS, 1 gm
DIFFERENCE

Oral cephalosporin efficacy with a once- or twice-a-day dosage

With DURICEF (cefadroxil), concentrations* in tonsillar tissue, urine, and skin blister fluid that exceed the MICs for susceptible organisms are significantly greater and/or longer lasting than those of cephalexin.[1-3]

This activity makes the difference between a q.i.d. regimen that's hard to remember and a simple once- or twice-a-day dosage that's hard to forget.[4]

*In vitro activity does not always correlate with in vivo effectiveness

Mead Johnson

For Brief Summary, please see following page.

SPECIAL CONTRIBUTION
anesthetic agents, cardiopulmonary
resuscitation, tissue perfusion

Artificial Perfusion Techniques During Cardiac Arrest: Questions of Experimental Focus Versus Clinical Need

James T. Niemann, MD
Torrance, California

From the UCLA School of Medicine, the Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California

Presented at the 1985 UAEM/RIEM Research Symposium in Orlando, Florida, February 7-8, 1985

Address for reprints: James T. Niemann, MD, Department of Emergency Medicine, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, California 90509

Contemporary cerebral-cardiopulmonary resuscitation investigations in the experimental laboratory have defined mechanisms for blood flow during closed-chest CPR and have demonstrated that the current CPR technique produces limited systemic perfusion. Modified closed-chest CPR techniques usually improve perfusion. Unfortunately few laboratory CPR studies have actually investigated resuscitation and survival. In addition, the animal model employed (prolonged ventricular fibrillation) may have limited clinical relevance, based on clinical experience and resuscitation practice, and data reporting techniques and their interpretation may be affected by control values that are not normal because of the effects of anesthetics. Closed-chest CPR was intended to buy time until a countershock could be delivered. Clinical and laboratory experience indicate that this goal can be met. Cerebral perfusion during closed-chest CPR is low, but adequacy from a functional perspective following restoration of circulation has not been carefully studied. Preservation of neuronal integrity after restoration of spontaneous circulation may be more important than cerebral perfusion during cardiac arrest and CPR. The role and benefit of open-chest CPR have yet to be determined, because this technique will most likely be used after conventional CPR failure. New and different experimental models are required to meet clinical needs and challenges. The alliance between practitioner and investigator should be strengthened if common goals are to be attained. [Niemann JT: Artificial perfusion techniques during cardiac arrest: Questions of experimental focus vs clinical need. Ann Emerg Med August 1985;14:761-768.]

Introduction

Recent physiological observations in the experimental laboratory suggest that systemic perfusion during closed-chest cardiopulmonary resuscitation (CPR) results from phasic fluctuations in intrathoracic pressure, rather than from selective compression of the cardiac ventricles between the sternum and spine.[1-3] Changes in intrathoracic pressure are transmitted equally to the cardiac chambers, the great intrathoracic vessels, and the peripheral arterial tree. Large peripheral arteriovenous pressure gradients necessary for systemic perfusion are found only in vascular beds protected by competent venous valves. Such valves allow a lower pressure to be maintained in the venous system of the tissue vasculature.[2-4]

These and other observations[5-7] made in the experimental laboratory and confirmed in electrical/computer models of arrested circulation[8] have given rise to the term "new CPR." In a strict sense, this term may indeed be applied to a new understanding and appreciation of the physiology of artificial circulatory support during cardiac arrest. A number of CPR techniques have been described that make use of this new knowledge and, in the laboratory, offer hemodynamic advantages over CPR as it is currently practiced in the clinical setting.[2,3,9,10] Unfortunately it is these new techniques, rather than the appreciation of a new and tenuous knowledge, that have attracted the attention of the lay public and the medical community. Practicing clinicians who deal with cardiac arrest daily recognize that the outcome of current CPR technique is poor in certain patient populations. CPR researchers and the clinical community believe that resuscitation outcome from cardiac arrest (particularly prehospital sudden cardiac death) could be better, based on

TABLE 1. *Outcome of prehospital arrest due to VF/VT*

	No. Patients	Witnessed	CPR	Admitted	In-Hospital Mortality	Discharged
Thompson[27] (Seattle, 1979)	316	76%	Early 34%	67%	36%	43%
			Late 66%	61%	66%	21%
Tweed[28] (Winnipeg, 1980)	226	NR*	Early 29%	45%	45%	25%
			Late 71%	25%	80%	5%
Guzy[29] (Los Angeles, 1983)	115	41%	Early 39%			27%
			Late 61%			6%
Roth[30] (Pittsburgh, 1984)	98	NR	Early 30%	48%	50%	23%
			Late 70%	24%	71%	12%

*Not reported

their recently acquired knowledge of hemodynamic findings and regional perfusion during modified CPR.

It seems appropriate at this time that clinician/CPR researchers return to their roots in clinical practice to examine the focus and relevance of research efforts from a clinical perspective. This discussion will address some questions of importance regarding the clinical applicability of resuscitation research findings and focus.

What Is the Purpose of CPR?

Recent experimental observations not only have defined a new mechanism for blood flow during conventional CPR, but also have called attention to the fact that conventional closed-chest CPR produces limited systemic perfusion. Modified closed-chest CPR techniques, based on new physiologic knowledge, also may be incapable of sustaining vital organ perfusion and life during cardiac arrest, though still producing better perfusion.[11]

The introduction of closed-chest CPR to clinical medicine was accepted rapidly despite limited (by contemporary standards) experimental study. Kouwenhoven and Knickerbocker, appropriately credited for discovering and recognizing the potential utility of closed-chest CPR,[12] were engineers engaged in the study of a technique for closed-chest electrical defibrillation. They noted that, "Our experience has indicated that external defibrillation is not likely to be followed by the return of spontaneous heart action, unless the countershock is applied within less than three minutes after the onset of ventricular fibrillation." Closed-chest countershock was not likely to be effective unless applied early. This limitation obviously would affect the importance and clinical applicability of their research findings. Contemporary research in the laboratory suggests that countershock of ventricular fibrillation (VF) of greater than two to three minutes duration without artificial circulatory support is unlikely to result in restoration of spontaneous circulation.[13-15]

Subsequent studies by Kouwenhoven et al were undertaken to assess the effects of rhythmic chest compression on defibrillation outcome. Earlier experiments had demonstrated that rhythmic chest compressions during VF produced arterial pressure pulses and arterial blood flow. Using the chest compression technique, Kouwenhoven and coworkers noted that, "A safe and effective method of massaging the heart without thoractomy was developed. *Adequate* circulation for periods as long as 30 minutes was easily maintained with the dog in ventricular fibrillation. A closed-chest defibrillating shock would result in the immediate return of normal sinus rhythm in such animals."[12]

The purpose of closed-chest CPR, as envisioned by its progenitors, was to provide *adequate* artificial circulation to the myocardium during VF until a closed-chest countershock could be administered. Adequate myocardial flow was defined only in terms of response to countershock; cerebral perfusion and preservation were implied, but never studied. Neither actual coronary blood flow nor regional myocardial perfusion was measured. Contemporary investigations of prolonged periods of VF and closed-chest CPR (up to one hour) have shown that regional myocardial flow or coronary perfusion pressures are low during prolonged CPR.[6,7,9,16-19] In addition, myocardial and cerebral blood flow may fall to nearly zero after two to five minutes of VF and CPR.[19,20]

Prolonged CPR is not, however, the treatment of choice for VF. The treatment of choice for VF is electrical countershock administered as soon as possible. From a clinical viewpoint, prolonged studies of CPR in the setting of VF are of limited clinical relevance. Evaluation of flow measurements has gained more attention than evaluation of adequacy (ie, restoration of circulation and long-term survival), even though a model to study adequacy is easily produced. Although electrical countershock is the treatment of choice for VF, only a few contemporary research studies actually have assessed countershock outcome and even these studied prolonged VF.[9,18,19,21-24] Only three studies have addressed long-term (more than 24-hour) survival.[21-23]

In sum, the investigative model most frequently used does not reflect the clinical practice of resuscitation. The clinician would not deny immediate countershock to the victim of VF. CPR researchers do.

Does Early CPR, as Currently Practiced, Affect Survival from Prehospital Sudden Cardiac Death?

Determinants of resuscitation outcome from prehospital[24] and inhospital[25] cardiac arrest only recently have been defined, and were not considered or reported in many early clinical studies.[26] Among these determinants are the initially encountered

TABLE 2. *Outcome of prehospital arrest due to rhythms other than VF/VT*

	No. Patients	Witnessed	CPR	Admitted	In-Hospital Mortality	Discharged
Myerburg[31] (Miami, 1980)	108	NR*	NR	8%	100%	0%
Guzy[29] (Los Angeles, 1983)	243	41%	Early 38%	NR	NR	17%
			Late 62%	NR	NR	4%
Roth[30] (Pittsburgh, 1984)	78	NR	Early 13%	20%	100%	0%
			Late 87%	21%	86%	3%

*Not reported.

cardiac rhythm disturbance, the availability of early CPR and countershock, the response time of advanced rescuers, and whether the patient's collapse was witnessed.

VF is reported to be the most common cause of prehospital sudden cardiac death, and most clinical studies addressing resuscitation outcome include only those patients in VF. Four representative clinical studies addressing outcome of prehospital cardiac arrest are summarized (Table 1). These studies were chosen for analysis for the following reasons: 1) only those patients in VF or ventricular tachycardia (VT) were studied; 2) response times for advanced rescuers were reported and were comparable; 3) the study population could be separated into those who received early CPR (usually by a bystander) and those who received late CPR (usually by a paramedic); and 4) hospital admission rates and survival rates were provided to allow calculation of inhospital mortality. For comparison, similar data available for patients found in rhythms other than VF or VT are shown (Table 2).

The following conclusions are supported by these clinical studies: 1) discharge rates of patients who receive early CPR (30 ± 9%) are substantially better than discharge rates of patients who do not receive early CPR (11 ± 7%); 2) survival from prehospital VF is more likely than survival from bradyasystole or other rhythms; 3) approximately 50% of patients found in VF will respond to current resuscitative practices and will survive to be admitted to the hospital; and 4) inhospital mortality of initially resuscitated patients is high and contributes substantially to overall prehospital arrest mortality.

Available data indicate that early CPR and countershock of VF in the setting of prehospital arrest improves survival chances and is not detrimental to a favorable outcome (survival to discharge). Although not addressed in most studies, preliminary data suggest that a substantial number of VF patients treated with prehospital countershock succumb to asystole post-countershock (35%).[32,33] When outcome has been studied, indications are that early CPR in the setting of prehospital bradyasystole may not affect survival.[33] Early CPR facilitates resuscitation from VF, but not from other rhythms.

One clinical investigator has suggested that the major effect of early CPR is prevention or attenuation of anoxic brain damage and its attendant complications, which increase inhospital mortality after initial cardiac resuscitation.[27] Early CPR may, in fact, have less effect on the chance of initial effective cardiac resuscitation than hoped. If resuscitation efforts do result in a spontaneous, perfusing cardiac rhythm, however, individuals who receive early CPR are more likely to leave the hospital alive (Table 1). Suggestions provided from the clinical population (ie, that early CPR facilitates cerebral preservation) are not necessarily in conflict with observations made in the experimental laboratory in studies of extended periods of circulatory arrest.

Do Experimental Models of Cardiac Arrest Reflect Clinical Experience?

Most clinical studies addressing resuscitation have evaluated emergency treatment of out-of-hospital cardiac arrest due to VF. The choice of the patient population has been dictated largely by the focus of the study, which is usually the utility of early countershock provided by paramedics or defibrillator-trained emergency medical technicians. VF is a favorable rhythm to study. As is the case with the forward pass in football, at least one of the three possible outcomes of VF countershock is "good", ie, restoration of spontaneous circulation. The other two outcomes, persistent VF and asystole or a pulseless rhythm, are accompanied by lower survival rates.[32,33] These other two outcomes, which may lower survival statistics substantially, have not been studied in the experimental laboratory as specifically appropriate tests of modified CPR techniques, and have been addressed infrequently by clinical investigators.

Asystole or a pulseless bradyarrhythmia is the rhythm encountered first in 30% to 50% of victims of prehospital sudden cardiac death.[30,31] It is nearly always fatal, and its treatment has not been addressed adequately by clinical or basic science investigators. The "utility" of pharmacologic agents used in the treatment of such rhythms largely rests on their effectiveness in VF or in pulseless bradyarrhythmias following asphyxia.[34,35] These pharmacologic interventions have not been well substantiated as beneficial in postcountershock or in initial asystole/pulseless bradyarrhythmia. The prevalence and mechanisms of cardiac arrest due to asystole or pulseless bradyarrhythmia have not been well established.[36] Resuscitation failure in these clinical situations accounts for most deaths due to prehospital cardiac arrest and deserves basic science and clinical study.

Is Vital Organ Perfusion During CPR Really That Bad?

Perception of the adequacy of ar-

TABLE 3. *Regional blood flow during prolonged VF and conventional CPR in dogs anesthetized with pentobarbital*

		MAP	CO	MBF	CBF	CPR Duration
	C	126	NR	200	190	
Luce*[6]	CPR		NR	7	14	7 min
	%C		—	4%	7	
	C	NR	254 mL/min/kg	144	211	
Voorhees[9]	CPR		23 mL/min/kg	22	25	30 min
	%C		9%	15%	12%	
	C	> 130	2,906 mL/min	119	211	
Ditchey[17]	CPR		327 mL/min	24	84	10 min
	%C		11%	20%	40%	
	C	108	NR	NR	NR	
Ralston[18]	CPR		27 mL/min/kg	24	23	10-20 min
	%C		—	—	—	
	C	> 130	NR	120 (LV)	36	
Michael[19]	CPR		NR	5 (LV)	1	< 5 min
	%C		—	4%	3%	
	C	NR	175 mL/min/kg	100	60	
Voorhees[37]	CPR		47 mL/min/kg	35	55	5 min
	%C		27%	35% (LV)	90%	

All values reported as the mean.
*Conventional CPR not performed in accordance with AHA guidelines.
C = control.
%C = percentage control.
CPR = conventional CPR.
CBF = cerebral blood flow (mL/min/100 g).
CO = cardiac output.
MAP = mean arterial pressure (mm Hg).
MBF = myocardial blood flow (mL/min/100 g).
NR = not reported.

tificial perfusion techniques during cardiac arrest is based largely on the study design and the data reporting methods of CPR investigators. Most CPR studies undertaken in the laboratory have not really studied definitive resuscitation or survival and functional status after resuscitation from cardiac arrest.

In the typical CPR experiment, "control" or prearrest flows and intravascular pressures are measured, VF is induced electrically, and conventional CPR is performed for a variable period of time, during which flows and pressures are measured. Conventional CPR often is compared to one or more other artificial perfusion techniques. Actual CPR flows and pressures are measured and reported. Defibrillation is attempted infrequently.

CPR flow and pressure data usually are reported as a "percentage of control" (relative measurements) to provide a foundation for comparison. The reader assumes that control means normal; however, this is not often the case. Our perception of the adequacy of conventional CPR as an artificial perfusion technique in the setting of cardiac arrest has been shaped by its comparison to the "normal" circulation. Cardiac output during conventional CPR is usually less than 30% of "normal," myocardial flow less than 20% of "normal," and cerebral flow less than 20% of "normal." Although such flows are abnormally low, they might be adequate, as initially postulated by Kouwenhoven and coworkers.

Anesthetized dogs, the most common study model in CPR research, are not "normal." At our institution, cardiac function of conscious dogs has been studied for ten years. Chronically instrumented dogs undergoing ventriculography and hemodynamic study (arterial pressure and indocyanine green cardiac output determinations) typically have a heart rate of 80 to 110 beats per minute, a mean arterial pressure of 100 mm Hg, and a cardiac output of 2.5 to 3.5 L/min (about 100 mL/min/kg). CPR animal research necessitates anesthesia, and pentobarbital is most frequently chosen. In the dose used, anesthesia, as well as a wide variety of "normal" or "control" measurements, are produced (Table 3).

Cardiac output in CPR experiments is reported using different units, and thus it is difficult to compare studies. In the first study by Voorhees,[37] cardiac output was measured in five controls and compared to 14 animals undergoing CPR. In three studies, control output was not reported. In a subsequent study by Voorhees,[9] control cardiac output was almost 50% more than in a previous study.[37]

In our experience, pentobarbital characteristically produces a sinus tachycardia and an elevated mean arterial pressure. Mean arterial pressures in the control state of CPR experiments are high, compared to observations made in conscious dogs. Control heart rates have not been reported, but rates greater than 140 beats per minute are usual in our experience. Heart

TABLE 4. *Regional blood flow during VF and conventional CPR in animals not anesthetized with pentobarbital*

		HR	MAP	CO	MBF	CBF	CPR Duration
	C	NR	79	2,306 mL/min	98	NR	
Bellamy*[16]	CPR	—	33	692 mL/min	20	NR	20 min
	%C	—	42%	35%	21%	—	
	C	138	110	3.04 L/min	179	42	
Shariff*[20]	CPR	—	—	NR	15	40	2 min
	%C	—	—	—	12%	95%	
	C	72	96	2,354 mL/min	40	NR	
Niemann†	CPR	—	47	NR	18	NR	2 min
	%C	—	49%	—	42%	NR	

All values reported as the mean.
*Swine model.
†Canine model (unpublished observations).
C = control.
CBF = cerebral blood flow (mL/min/100 g).
CPR = conventional CPR.
%C = percentage control.
CO = cardiac output.
HR = heart rate (beats/min).
MAP = mean arterial pressure (mm Hg).
MBF = myocardial blood flow (mL/min/100 g).
NR = not reported or not measured.

rate and arterial pressure are major determinants of myocardial oxygen demand and, therefore, coronary arterial flow and myocardial perfusion. Not unexpectedly, control myocardial flows in the CPR research laboratory (using pentobarbital anesthesia in dogs) range from 100 mL/min/100 g to 200 mL/min/100 g. A true normal or control state for comparison of CPR myocardial perfusion has not been established, resulting in a wide range of control values.

Similar differences in control values are seen when cerebral blood flow has been measured (microsphere technique). This has led to widely scattered values of flow during coventional CPR, when compared to the control (and presumably normal) state prior to induced cardiac arrest. For comparison, data from several recent studies using anesthetics other than pentobarbital are shown (Table 4). CPR hemodynamics were studied in swine in two of the investigations.[16,20]

When compared to the control setting (percentage of control), conventional CPR produces low and widely variable myocardial and cerebral perfusion. Although such flows are low compared to control values but not necessarily to normal values, only three contemporary studies have addressed their "adequacy" as defined by Kouwenhoven and coworkers, ie, restoration of spontaneous circulation after countershock.

We have suggested previously that myocardial flow during VF and CPR should approximate 20 mL/min/100 g to meet the metabolic demands of the fibrillating heart and facilitate resuscitation.[11] The studies of Ralston et al[18] (20 minutes of VF and CPR) and Michael et al[19] (50 minutes of VF and CPR) suggest that if myocardial flow can be maintained at values ≥ 20 mL/min/100 g during the period of VF, countershock will result in a perfusing rhythm despite prolonged VF and CPR. In an unpublished study from our laboratory, coronary flows of 15 mL/min/100 g during conventional CPR resulted in restoration of spontaneous circulation in the setting of postcountershock asystole or pulseless bradyarrhythmia.

Although myocardial flow was low in these three studies (when compared to percentage of control flow), spontaneous circulation was restored. If a flow value of about 20 mL/min/100 g of myocardial tissue is accepted as adequate (ie, will result in restoration of circulation after countershock), then in five of seven studies in which myocardial perfusion was measured during varying periods of VF and CPR, countershock did or could have resulted in definitive cardiac resuscitation. (Tables 3 and 4).

As envisioned by its progenitors 25 years ago, early CPR after VF may provide adequate myocardial flow, ie, adequate to facilitate restoration of circulation after early countershock, for periods up to 30 minutes long. From this perspective, conventional CPR myocardial flow may indeed be life-sustaining.

Cerebral Perfusion During CPR: How Much is Needed to Assure an Acceptable Functional Status After Cardiac Resuscitation?

The question of how much cerebral perfusion is needed during CPR has not been addressed adequately by contemporary CPR investigators. Long-term survival after cardiac arrest and conventional CPR has been studied infrequently, and the cerebral flow necessary during CPR for grossly normal neurologic function in animals after restoration of spontaneous circulation has not been reported. Cerebral blood flow of only 20% to 30% of normal may be all that is required to maintain the brain's viability as assessed by electrical activity.[48,49] Normal or "control" cerebral flow varies from study to study, however (Table 3), and obviously will affect percentage of

control measurements during cardiac arrest and artificial circulatory support. Nonetheless, percentage of control data has received the greatest attention. Relating neurologic outcome to a given flow (flow per gram or 100 grams of tissue) would provide uniformity, permit comparison of studies, and allow the clinician and investigator to attach functional significance to flow values.

Similarly, cerebral metabolites may not be a reliable index of return of neurologic function.[40] Whether brain mitochondrial metabolic function following ischemia is directly related to return of neurologic function in the intact organism has not been thoroughly assessed by investigative laboratories. The current controversy regarding complete versus incomplete cerebral ischemia[41] may be related partly to what is being measured (ie, cellular metabolites, mitochondrial metabolic function, or functional neurologic outcome, which can only be assessed by gross techniques in animals without higher cognitive capabilities).

The ultrastructural and biochemical events associated with irreversible cell death are being defined and scrutinized in elegant experiments, and there is a growing body of knowledge that suggests that many processes resulting in cell death may occur after reperfusion of previously ischemic tissue.[41-44] Prevention of postreperfusion cellular injury and death perhaps can be accomplished pharmacologically. If so, preservation of neuronal integrity after restoration of spontaneous circulation may be more important than cerebral perfusion during cardiac arrest and CPR. Preventing postreperfusion injury to the heart and brain, if it is indeed possible using pharmacologic agents, could substantially increase hospital discharge rates of victims of prehospital or inhospital cardiac arrest, without changing CPR techniques to treat the typical victim of cardiac arrest (sudden death due to VF).

Open-Chest Direct Cardiac Massage — Will It Improve Outcome from Cardiac Arrest?

Experimental studies in animal models have shown consistently that open-chest CPR, or direct cardiac massage, is hemodynamically superior to closed-chest CPR in the setting of prolonged VF. In the experimental model of prolonged VF, open-chest CPR is capable of maintaining flow to vital organs at a level nearly equal to prearrest or control state. Prolonged open-chest CPR during VF, followed by countershock, results in better long-term outcome than does conventional CPR.[23] Such outcomes are expected, because the hemodynamic effects of manual, selective ventricular compression closely approximate those of a spontaneous ventricular systole or contraction. The hemodynamic effects of closed-chest thoracic compression are different, and reflect differences in the mechanism of antegrade left heart outflow.[45,46] Better regional flow and outcome during open-chest CPR in the setting of prolonged VF is a fact and cannot be rationally debated.

What is unresolved is the role that open-chest CPR will play in resuscitation, particularly resuscitation from prehospital cardiac arrest. The laboratory experience is artificial in that VF has been studied for prolonged periods without defibrillation, the treatment of choice. Contemporary laboratory experience cannot be directly translated to the clinical setting, and the choice of the prolonged VF study model may have biased outcome and the medical community's perception of the effectiveness of closed-chest CPR.

Proponents of open-chest CPR frequently cite the experience of Stephenson and colleagues.[47] This study addresses some common denominators in 1,200 cases of cardiac arrest treated with open-chest CPR. Only 133 of the 1,200 patients (12%) arrested due to VF. Eighty-four (63%) were successfully defibrillated using direct epicardial countershock. Thirty-nine (29%) survived to be discharged from the hospital. There was an inhospital mortality rate of 56% following initial successful resuscitation. These numbers are comparable to contemporary prehospital resuscitation experience (Table 1), despite the use of direct cardiac massage within four minutes of arrest. We do not know if differences in postresuscitation care over three decades could further affect survival outcome. Of note is that when early closed-chest CPR and defibrillation from VF can be provided within four minutes of arrest, hospital discharge rates may exceed 40%.[30] Thus the clinical data suggest that early artificial circulatory support (combined with early countershock) is equally efficacious with either the open-chest or closed-chest technique.

The majority of the patients in Stephenson's study suffered circulatory arrest due to rhythms other than VF. Arrest was ascribed to "vaso-vagal reflex action" or was the result of administered anesthetics. Open-chest CPR resulted in a hospital discharge rate of 28% in this population. This outcome substantially exceeds the outcome of closed-chest CPR in prehospital arrests due to rhythms other than VF. The populations are dissimilar, however, and cannot be directly compared.

Currently there are no data to support the efficacy of early open-chest CPR over early closed-chest CPR when either is combined with early countershock. The utility of open-chest CPR after failed closed-chest resuscitation techniques has not been adequately studied, but available experimental data suggest that use of open-chest CPR after 20 minutes of arrest is unlikely to result in improved outcome.[48] The use of open-chest CPR in prehospital arrest rhythms other than VF has not been studied, but could be advantageous.

Clinical Experience vs Experimental Models: Is There a Difference? Defining Clinical Needs

The treatment of prehospital VF may be less than optimal and constricted by current practice. Outcome is dependent on the early availability of artificial circulatory support and countershock. The unavailability of early conventional CPR may not be used to belie its effectiveness.

Mortality from prehospital cardiac arrest due to VF can be accounted for by the following: 1) delay in defibrillation;[24,26,30] 2) postcountershock or "secondary" asystole/bradycardia; and 3) inhospital mortality or morbidity after restoration of spontaneous circulation. In a recent study, investigators defined a population at risk for postcountershock asystole/bradycardia.[32] Experimental data suggest that postresuscitation and postreperfusion tissue injury can be prevented or attenuated. In a population of patients with VF, radical alteration in artificial perfusion techniques may not be necessary because morbidity and mortality can be prevented.

Arrest rhythms other than VF or

VT are usually fatal. This result is expected because of a limited understanding of their mechanism and, therefore, their treatment. Such rhythms may account for as many as 50% of prehospital resuscitation failures. These failures may not be ascribed to the perceived inadequacies of conventional CPR, because closed-chest CPR was advocated by its inventors to buy time until closed-chest countershock could be made available. The mechanism of primary bradyasystolic arrest are poorly understood, but their importance is recognized. In contrast to VF, there is no prescribed treatment of value, even when non-VF arrest occurs when advanced rescuers are present.[30,49]

The clinical needs of practitioners demand the development and study of primary bradyasystolic models of cardiac arrest; attention to postresuscitative care of survivors of prehospital cardiac arrest; predictors and treatment of postcountershock asystole/pulseless bradyarrhythmias; definition of the "window" for cardiac resuscitation in the clinical setting; and clarification of the utility of unconventional circulatory support techniques in conventional resuscitation failures. The outcome and the importance of an alliance between the practitioner and the basic investigator is obvious, and it must be cultivated if current resuscitation research is to achieve its intended purpose, that is, patient benefit.

References

1. Rudikoff MT, Maughan WL, Effron M, et al: Mechanisms of blood flow during cardiopulmonary resuscitation. *Circulation* 1980;61:345-352.

2. Niemann JT, Rosborough JP, Hausknecht M, et al: Pressure-synchronized cineangiography during experimental cardiopulmonary resuscitation. *Circulation* 1981;64:985-991.

3. Werner JA, Greene HL, Janko CL, et al: Visualization of cardiac valve motion in man during external chest compression using two-dimensional echocardiography. Implications regarding the mechanism of flow. *Circulation* 1981;63:1417-1421.

4. Fisher L, Baghaiwalla F, Tsitlik J, et al: Determinants and clinical significance of jugular venous valve competence. *Circulation* 1982;65:188-196.

5. Chandra N, Weisfeldt ML, Tsitlik J, et al: Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressure simultaneous with chest compression. *Am J Cardiol* 1981;48:1053-1063.

6. Luce JM, Ross BK, O'Quin RJ, et al: Regional blood flow during cardiopulmonary resuscitation in dogs using simultaneous and nonsimultaneous compression and ventilation. *Circulation* 1983;67:258-265.

7. Koehler RC, Chandra N, Guerci AD, et al: Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. *Circulation* 1983;67:266-275.

8. Babbs CF, Weaver JC, Ralston SH, et al: Cardiac, thoracic, and abdominal pump mechanisms in cardiopulmonary resuscitation: Studies in an electrical model of the circulation. *Am J Emerg Med* 1984;2:299-308.

9. Voorhees WD, Ralston SH, Babbs CF: Regional blood flow during cardiopulmonary resuscitation with abdominal counterpulsation in dogs. *Am J Emerg Med* 1984;2:123-128.

10. Maier GW, Tyson GS, Olsen GO, et al: The physiology of external cardiac massage: High-impulse cardiopulmonary resuscitation. *Circulation* 1984;70:86-101.

11. Niemann JT: Differences in cerebral and myocardial perfusion during closed-chest resuscitation. *Ann Emerg Med* 1984;13(II):849-853.

12. Kouwenhoven WB, Jude JR, Knickerbocker GG: Closed-chest cardiac massage. *JAMA* 1960;173:1064-1067.

13. Ewy GA: Defining electromechanical dissociation. *Ann Emerg Med* 1984;13(II):830-832.

14. Vincent JL, Thijs L, Weil MH, et al: Clinical and experimental studies on electromechanical dissociation. *Circulation* 1981;64:18-27.

15. Niemann JT, Garner DA, Rosborough JP: Endocardial and transcutaneous cardiac pacing, calcium chloride, and epinephrine in postcountershock asystole and pulseless bradyarrhythmias. *Crit Care Med*, in press.

16. Bellamy RF, DeGuzman LR, Pedersen DC: Coronary blood flow during cardiopulmonary resuscitation in swine. *Circulation* 1984;69:174-180.

17. Ditchey RV, Lindenfeld J: Potential adverse effects of volume loading on perfusion of vital organs during closed-chest resuscitation. *Circulation* 1984;69:181-189.

18. Ralston SH, Voorhees WD, Babbs CF: Intrapulmonary epinephrine during prolonged cardiopulmonary resuscitation: Improved regional flow and resuscitation in dogs. *Ann Emerg Med* 1984;13:79-86.

19. Michael JR, Guerci AD, Koehler RC, et al: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984;69:822-835.

20. Sharff JA, Pantley G, Noel E: Effect of time on regional organ perfusion during two methods of cardiopulmonary resuscitation. *Ann Emerg Med* 1984;13:649-656.

21. Niemann JT, Rosborough JP, Niskanen RA, et al: Mechanical "cough" cardiopulmonary resuscitation in dogs. *Am J Cardiol* 1985;55:199-204.

22. Kern KB, Carter AB, Showan L, et al: Resuscitation and twenty-four hour survival among three different modes of manual cardiopulmonary resuscitation, abstract. *Clin Res* 1985;33:10A.

23. Bircher N, Safar P: Manual open-chest cardiopulmonary resuscitation. *Ann Emerg Med* 1984;13(II):770-773.

24. Eisenberg M, Hallstrom A, Bergner L: The ACLS score: Predicting survival from out-of-hospital cardiac arrest. *JAMA* 1981;246:50-52.

25. Bedell SE, Delbanco TL, Cook EF, et al: Survival after cardiopulmonary resuscitation in the hospital. *N Engl J Med* 1983;309:569-576.

26. Eisenberg MS, Bergner L, Hearne T: Out-of-hospital cardiac arrest: A review of major studies and a proposed uniform reporting system. *Am J Public Health* 1980;70:236-240.

27. Thompson RG, Hallstrom AP, Cobb LA: Bystander initiated cardiopulmonary resuscitation in the management of ventricular fibrillation. *Ann Intern Med* 1979;90:737-740.

28. Tweed WA, Bristow G, Donen N: Resuscitation from cardiac arrest: Assessment of a system providing only basic life support outside of hospital. *Can Med Assoc J* 1980;122:297-300.

29. Guzy PM, Pearce ML, Greenfield S: The survival benefit of bystander cardiopulmonary resuscitation in a paramedic-served metropolitan area. *Am J Public Health* 1983;73:766-796.

30. Roth R, Stewart RD, Rogers K, et al: Out-of-hospital cardiac arrest: Factors associated with survival. *Ann Emerg Med* 1984;13:237-243.

31. Myerburg RJ, Conde CA, Sung RJ, et al: Clinical, electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. *Am J Med* 1980;68:568-576.

32. Weaver WD, Cobb LA, Dennis D, et al: Amplitude of ventricular fibrillation wave form and outcome after cardiac arrest. *Ann Intern Med* 1985;102:53-55.

33. Weaver WD, Cobb LA, Copass MK, et al: Ventricular defibrillation: A comparative trial using 175-J and 320-J. *N Engl J Med* 1982;307:1101-1106.

34. Redding JS, Pearson JW: Resuscitation from asphyxia. *JAMA* 1962;182:283-286.

35. Redding JS, Pearson JW: Resuscitation

from ventricular fibrillation. *JAMA* 1968; 203:255-260.

36. Greenberg HM: Bradycardia at onset of sudden death: Potential mechanisms. *Ann NY Acad Sci* 1984;427:241-252.

37. Voorhees WD, Babbs CF, Tacker WA: Regional blood flow during cardiopulmonary resuscitation in dogs. *Crit Care Med* 1980;8:134-136.

38. Astrup J, Symon L, Branston NM, et al: Cortical evoked potential in extracellular K^+ and H^+ at critical levels of brain ischemia. *Stroke* 1977;8:51-57.

39. Sundt TM, Sharbrough FW, Piepgras DC, et al: Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: With results of surgery and hemodynamics of cerebral ischemia. *Mayo Clin Proc* 1981; 56:533-543.

40. Steen PA, Michenfelder JD, Milde JH: Incomplete cerebral ischemia: Improved outcome with minimal blood flow. *Ann Neurol* 1979;6:389-398.

41. Newberg LA: Cerebral resuscitation: Advances and controversies. *Ann Emerg Med* 1984;13(II):853-856.

42. White BC: Brain injury by ischemic anoxia: Hypothesis extension-A tale of two ions? *Ann Emerg Med* 1984;13(II): 862-867.

43. Gadzinski DS, White BC, Hoehner PJ, et al: Alterations in canine cerebral cortical blood flow and vascular resistance post cardiac arrest. *Ann Emerg Med* 1982;11:58-63.

44. White BC, Gadzinski DS, Hoehner PJ, et al: Effect of flunarizine on canine cerebral cortical blood flow and vascular resistance post cardiac arrest. *Ann Emerg Med* 1982;11:119-126.

45. Chandra N, Guerci A, Weisfeldt ML, et al: Contrasts between intrathoracic pressures during external chest compression and cardiac massage. *Crit Care Med* 1981;9:789-792.

46. Weisfeldt ML, Chandra N, Tsitlik J: Increased intrathoracic pressure-not direct heart compression-causes the rise in intrathoracic vascular pressures during CPR in dogs and pigs. *Crit Care Med* 1981;9:377-378.

47. Stephenson HE, Reid LC, Hinton JW: Some common denominators in 1,200 cases of cardiac arrest. *Ann Surg* 1953; 137:731-744.

48. Sanders AB, Ewy GA: Open-chest CPR: Not yet, editorial. *Am J Emerg Med* 1984;2:566-567.

49. Iseri LT, Humphrey SB, Siner EJ: Prehospital brady-asystolic cardiac arrest. *Ann Intern Med* 1978;88:741-745.

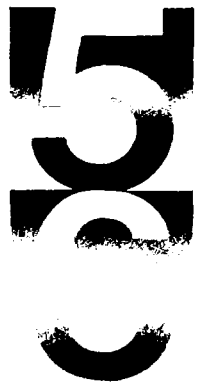
An extended-spectrum cephalosporin with the benefits of three generations —and more

Once-a-day

24-hr kill power

Broad and practical spectrum

Wide utility



Established safety

Cost effective

ROCHE

An extended-spectrum cephalosporin with the benefits of three generations —and more

[redacted] for 24 hours,

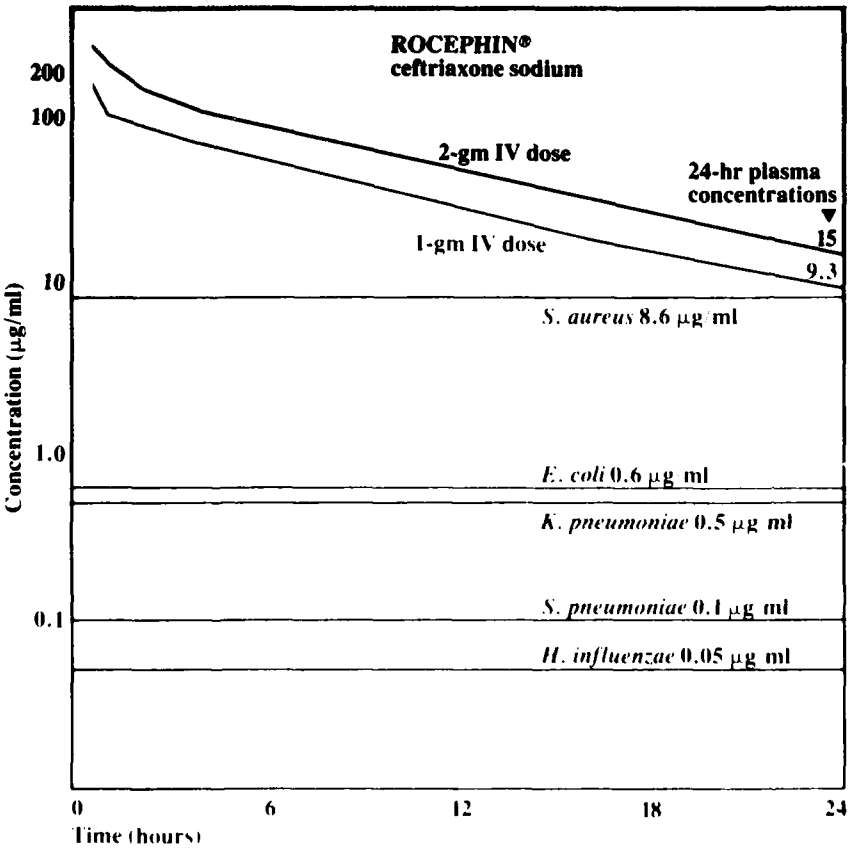
[redacted] sputum,[2] lung tissue,[3] cerebrospinal [redacted] pericardial fluid,[2] and bile,[4] as well as in bone.[2]

[redacted] regarded as important to therapeutic efficacy, but specific concentrations may not necessarily correlate with therapeutic results.

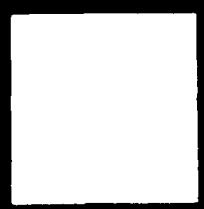
Usual adult dosage—1 gm to 2 gm once a day

24-hr kill power

Plasma levels are above minimum bactericidal concentrations (MBC_{90}s) of common pathogens for 24 hours;[1,5] plasma concentrations are regarded as important to therapeutic efficacy, but specific levels may not necessarily correlate with therapeutic results.



Once-a-day Rocephin® IV·IM ROCHE
ceftriaxone sodium/Roche



Type of infection	Bacteriologic cure: Total no. of isolates	Bacteriologic cure: % Eradicated	Clinical outcome: Total no. of diagnoses	Clinical outcome: % Cured	Clinical outcome: % Improved
Lower respiratory tract	288	96	242	75	20
Skin and skin structure	418	90	302	71	22
Urinary tract	235	99	217	91	9
Bacterial septicemia	114	99	111	93	6
Bone and joint	108	94	97	63	28
Intra-abdominal	30	87	26	73	15
Pelvic inflammatory disease (PID)	13	100	13	92	—
Uncomplicated gonorrhea	167	99	not reported	not reported	not reported
Meningitis and shunt infections	68	100	68	91	7
Prophylaxis in coronary artery bypass surgery	May reduce incidence of postoperative infection				

Plus... A single preoperative dose provides equivalent prophylaxis for coronary artery bypass surgery as compared with a multiple perioperative dosing regimen of cefazolin[1]

Bacteriologic cure
Eradication of the causative microorganism(s) identified in the pretreatment cultures

Clinical cure
Elimination of the clinical signs and symptoms of the disease, with no recurrence at the time the drug was discontinued or during follow-up.

Clinical improvement
A significant lessening of the clinical signs and symptoms of the disease.

Please see last pages of this advertisement for complete product information, including indicated susceptible organisms.

Once-a-day dosing in adults for greater savings—eliminates multiple pharmacy, preparation and administration costs

Severe infections can be treated with a single dose of 2 gm daily

Outpatient usage offers an additional opportunity for cost containment

How to prescribe Rocephin

Usual adult dose	1 to 2 gm, once a day, IV or IM
Pediatric meningitis	100 mg/kg (not to exceed 4 gm) in divided doses every 12 hours, with or without a loading dose of 75 mg/kg
Serious miscellaneous infections in children (other than meningitis)	50 to 75 mg/kg (not to exceed 2 gm) in divided doses every 12 hours
Uncomplicated gonococcal infections	Single 250-mg IM dose
Surgical prophylaxis: coronary artery bypass	Single 1-gm dose, ½ to 2 hours preoperatively

References:

1. Data on file, Hoffmann-La Roche Inc.
2. Richards DM, *et al: Drugs 27*:469-527, 1984.
3. Just H-M, *et al: Chemotherapy 30*:81-83, Mar/Apr 1984.
4. Patel IH, Kaplan SA: *Am J Med 77*:17-25, Oct 19, 1984.
5. Cleeland R, Squires E: *Am J Med 77*:3-11, Oct 19, 1984.

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Please see next pages for complete product information.

Once-a-day Rocephin® IV·IM

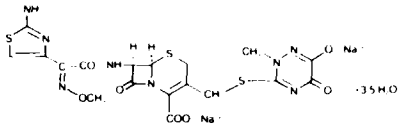
ROCHE

ceftriaxone sodium/Roche

Rocephin® IV·IM
ceftriaxone sodium/Roche

DESCRIPTION: Rocephin* (ceftriaxone sodium/Roche) is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6R-[6α,7β(Z)]]-.

The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59 and the following structural formula:



Rocephin is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of Rocephin solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Rocephin contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

CLINICAL PHARMACOLOGY: Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (I.V.) infusion of a 0.5, 1 or 2 gm dose and intramuscular (I.M.) administration of a single 0.5 or 1 gm dose in healthy subjects are presented in Table 1.

TABLE 1
Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (mcg/ml)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gm I.V.*	82	59	48	37	29	23	15	10	5
0.5 gm I.M.	30	41	43	39	31	25	16	ND†	ND
1 gm I.V.*	151	111	88	67	53	43	28	18	9
1 gm I.M.	40	68	76	68	56	44	29	ND	ND
2 gm I.V.*	257	192	154	117	89	74	46	31	15

*I.V. doses were infused at a constant rate over 30 minutes.
†ND = Not determined.

Ceftriaxone was completely absorbed following I.M. administration with mean maximum plasma concentrations occurring between two and three hours postdosing. Multiple I.V. or I.M. doses ranging from 0.5 to 2 gm at 12 to 24-hour intervals resulted in 15 to 36% accumulation of ceftriaxone above single dose values.

Ceftriaxone concentrations in urine are high, as shown in Table 2.

TABLE 2
Urinary Concentrations of Ceftriaxone After Single Dose Administration

Dose/Route	Average Urinary Concentrations (mcg/ml)					
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr	24-48 hr
0.5 gm I.V.	526	366	142	87	70	15
0.5 gm I.M.	115	425	308	127	96	28
1 gm I.V.	995	855	293	147	132	32
1 gm I.M.	504	628	418	237	ND*	ND
2 gm I.V.	2692	1976	757	274	198	40

*ND = Not determined.

Thirty-three to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 gm I.V. dose, average concentrations of ceftriaxone, determined from one to three hours after dosing, were 581 mcg/ml in the gallbladder bile, 788 mcg/ml in the common duct bile, 898 mcg/ml in the cystic duct bile, 78.2 mcg/gm in the gallbladder wall and 62.1 mcg/ml in the concurrent plasma.

Over a 0.15 to 3 gm dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours, apparent volume of distribution from 5.78 to 13.5 L, plasma clearance from 0.58 to 1.45 L/hour, and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of ~ 25 mcg/ml to a value of 85% bound at 300 mcg/ml.

The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg I.V. dose and after a 75 mg/kg I.V. dose in pediatric patients suffering from bacterial meningitis are shown in Table 3. Ceftriaxone penetrated the inflamed meninges of infants and children. CSF concentrations after a 50 mg/kg I.V. dose and after a 75 mg/kg I.V. dose are also shown in Table 3.

TABLE 3
Average Pharmacokinetic Parameters of Ceftriaxone in Pediatric Patients with Meningitis

	50 mg/kg I.V.	75 mg/kg I.V.
Maximum Plasma Concentrations (mcg/ml)	216	275
Elimination Half-life (hr)	4.6	4.3
Plasma Clearance (ml/hr/kg)	49	60
Volume of Distribution (ml/kg)	338	373
CSF Concentration – inflamed meninges (mcg/ml)	5.6	6.4
Range (mcg/ml)	1.3-18.5	1.3-44
Time after dose (hr)	3.7 (~1.6)	3.3 (~1.4)

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 gm per day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced, suggesting that plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

TABLE 4
Average Pharmacokinetic Parameters of Ceftriaxone in Humans

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy Subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly Subjects (mean age 70.5 yr)	8.9	0.83	10.7
Patients with renal impairment			
Hemodialysis patients (0.5 ml/min)*	14.7	0.65	13.7
Severe (5-15 ml/min)	15.7	0.56	12.5
Moderate (16-30 ml/min)	11.4	0.72	11.8
Mild (31-60 ml/min)	12.4	0.70	13.3
Patients with liver disease	8.8	1.1	13.6

*Creatinine clearance

ROCEPHIN* (ceftriaxone sodium/Roche)

MICROBIOLOGY: The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage):

GRAM-NEGATIVE AEROBES: *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*.

Note: Many strains of the above organisms that are multiply resistant to other antibiotics, *e.g.*, penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium.

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*.

GRAM-POSITIVE AEROBES: *Staphylococcus aureus* (including penicillinase-producing strains) and *Staphylococcus epidermidis* (Note: methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae*. (Note: Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant.)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown:

GRAM-NEGATIVE AEROBES: *Citrobacter freundii, Citrobacter diversus, Providencia* species (including *Providencia rettgeri*), *Salmonella* species (including *S. typhi*), *Shigella* species and *Acinetobacter calcoaceticus*.

ANAEROBES: *Bacteroides* species, *Clostridium* species (Note: most strains of *C. difficile* are resistant).

SUSCEPTIBILITY TESTING: Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45:493-496, 1966; Standardized Disk Susceptibility Test, *Federal Register* 39:19182-19184, 1974; National Committee for Clinical Laboratory Standards, Approved Standard ASM-2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975.) has been recommended for use with disks to *test susceptibility to ceftriaxone*.

Laboratory results of the standardized single-disk susceptibility test using a 30 mcg ceftriaxone disk should be interpreted according to the following three criteria:

1. Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (*e.g.*, urine), in which high antibiotic levels are attained.
3. *Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.*

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks.

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone.

Standardized procedures require use of control organisms. The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853, respectively.

DILUTION TECHNIQUES: Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml. Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml. Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (*e.g.*, urine), in which high antibiotic levels are attained.

E. coli ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests. Greater than 95% of MICs for the *E. coli* strain should fall within the range of 0.016 to 0.5 mcg/ml. The range for the *S. aureus* strain should be 1 to 2 mcg/ml, while for the *P. aeruginosa* strain the range should be 8 to 64 mcg/ml.

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*.

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*.

BONE AND JOINT INFECTIONS caused by Staph. aureus, Strep. pneumoniae, Streptococcus species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*.

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*.

PROPHYLAXIS: The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery. Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO *DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS.* THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*.

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: *GENERAL*: Although transient elevations of BUN and serum creatinine have been observed at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

ROCEPHIN® (ceftriaxone sodium Roche)

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed.

LOCAL REACTIONS — pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY — rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC — eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL — diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia.

HEPATIC — elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL — elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM — headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY — moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS — diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

DIRECTIONS FOR USE: *INTRAMUSCULAR ADMINISTRATION*: Reconstitute Rocephin powder with the appropriate diluent (see Compatibility/Stability section).

Vial Dosage Size	Amount of Diluent to be Added
250 mg	0.9 ml
500 mg	1.8 ml
1 gm	3.6 ml
2 gm	7.2 ml

ROCEPHIN® (ceftriaxone sodium Roche)

After reconstitution, each 1 ml of solution contains approximately 250 mg equivalent of ceftriaxone. If required, more dilute solutions could be utilized. As with all intramuscular preparations, Rocephin should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

INTRAVENOUS ADMINISTRATION: Rocephin should be administered intravenously by intermittent infusion. Concentrations between 10 mg/ml and 40 mg/ml are recommended; however, lower concentrations may be used if desired. Reconstitute vials or "piggyback" bottles with an appropriate I.V. diluent (see Compatibility/Stability section):

Vial Dosage Size	Amount of Diluent to be Added
250 mg	2.4 ml
500 mg	4.8 ml
1 gm	9.6 ml
2 gm	19.2 ml

After reconstitution, each 1 ml of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate I.V. diluent.

Piggyback Bottle Dosage Size	Amount of Diluent to be Added
1 gm	10 ml
2 gm	20 ml

After reconstitution, further dilute to 50 ml or 100 ml volumes with the appropriate I.V. diluent.

10 gm Bulk Pharmacy Container: This dosage size is *NOT FOR DIRECT ADMINISTRATION*. Reconstitute powder with 95 ml of an appropriate I.V. diluent. Before parenteral administration, withdraw the required amount, then further dilute to the desired concentration.

COMPATIBILITY AND STABILITY: Rocephin sterile powder should be stored at room temperature (up to 77°F/25°C) — or below and protected from light. After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Rocephin *intramuscular* solutions remain stable (loss of potency less than 10%) for the following time periods:

Diluent	Concentration mg/ml	Storage: Room Temp. (25°C)	Storage: Refrigerated (4°C)
Sterile Water for Injection	100	3 days	10 days
	250	24 hours	3 days
0.9% Sodium Chloride Solution	100	3 days	10 days
	250	24 hours	3 days
5% Dextrose Solution	100	3 days	10 days
	250	24 hours	3 days
Bacteriostatic Water + 0.9% Benzyl Alcohol	100	24 hours	10 days
	250	24 hours	3 days
1% Lidocaine Solution (without epinephrine)	100	24 hours	10 days
	250	24 hours	3 days

Rocephin *intravenous* solutions, at concentrations of 10, 20 and 40 mg/ml, remain stable (loss of potency less than 10%) for the following time periods stored in glass or PVC containers:

Diluent	Storage: Room Temp. (25°C)	Storage: Refrigerated (4°C)
Sterile Water	3 days	10 days
0.9% Sodium Chloride Solution	3 days	10 days
5% Dextrose Solution	3 days	10 days
10% Dextrose Solution	3 days	10 days
5% Dextrose + 0.9% Sodium Chloride Solution*	3 days	Incompatible
5% Dextrose + 0.45% Sodium Chloride Solution	3 days	Incompatible

*Data available for 10-40 mg/ml concentrations in this diluent in PVC containers only.

Similarly, Rocephin *intravenous* solutions, at concentrations of 100 mg/ml, remain stable in the I.V. piggyback glass containers for the above specified time periods.

The following *intravenous* Rocephin solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/ml and 40 mg/ml: Sodium Lactate (PVC container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container), Freamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers), Inosol-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10% Mannitol (glass container).

After the indicated stability time periods, unused portions of solutions should be discarded.

Rocephin reconstituted with 5% Dextrose or 0.9% Sodium Chloride solution at concentrations between 10 mg/ml and 40 mg/ml, and then stored in frozen state (−20°C) in PVC (Viaflex) or polyolefin containers, remains stable for 26 weeks.

Frozen solutions should be thawed at room temperature before use. After thawing, unused portions should be discarded. Do not refreeze.

Rocephin solutions should *not* be physically mixed with other antimicrobial drugs due to possible incompatibility.

ANIMAL PHARMACOLOGY: Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with ceftriaxone.

These appeared as a gritty sediment in dogs that received 100 mg/kg/day for four weeks. A similar phenomenon has been observed in baboons but only after a protracted dosing period (6 months) at higher dose levels (335 mg/kg/day or more). The likelihood of this occurrence in humans is considered to be low, since ceftriaxone has a greater plasma half-life in humans, the calcium salt of ceftriaxone is more soluble in human gallbladder bile and the calcium content of human gallbladder bile is relatively low.

HOW SUPPLIED: Rocephin (ceftriaxone sodium Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg equivalent of ceftriaxone sodium: Boxes of 10 (NDC 0004-1962-01).

Vials containing 500 mg equivalent of ceftriaxone sodium: Boxes of 10 (NDC 0004-1963-01).

Vials containing 1 gm equivalent of ceftriaxone sodium: Boxes of 10 (NDC 0004-1964-01).

Piggyback bottles containing 1 gm equivalent of ceftriaxone sodium: Boxes of 10 (NDC 0004-1964-03).

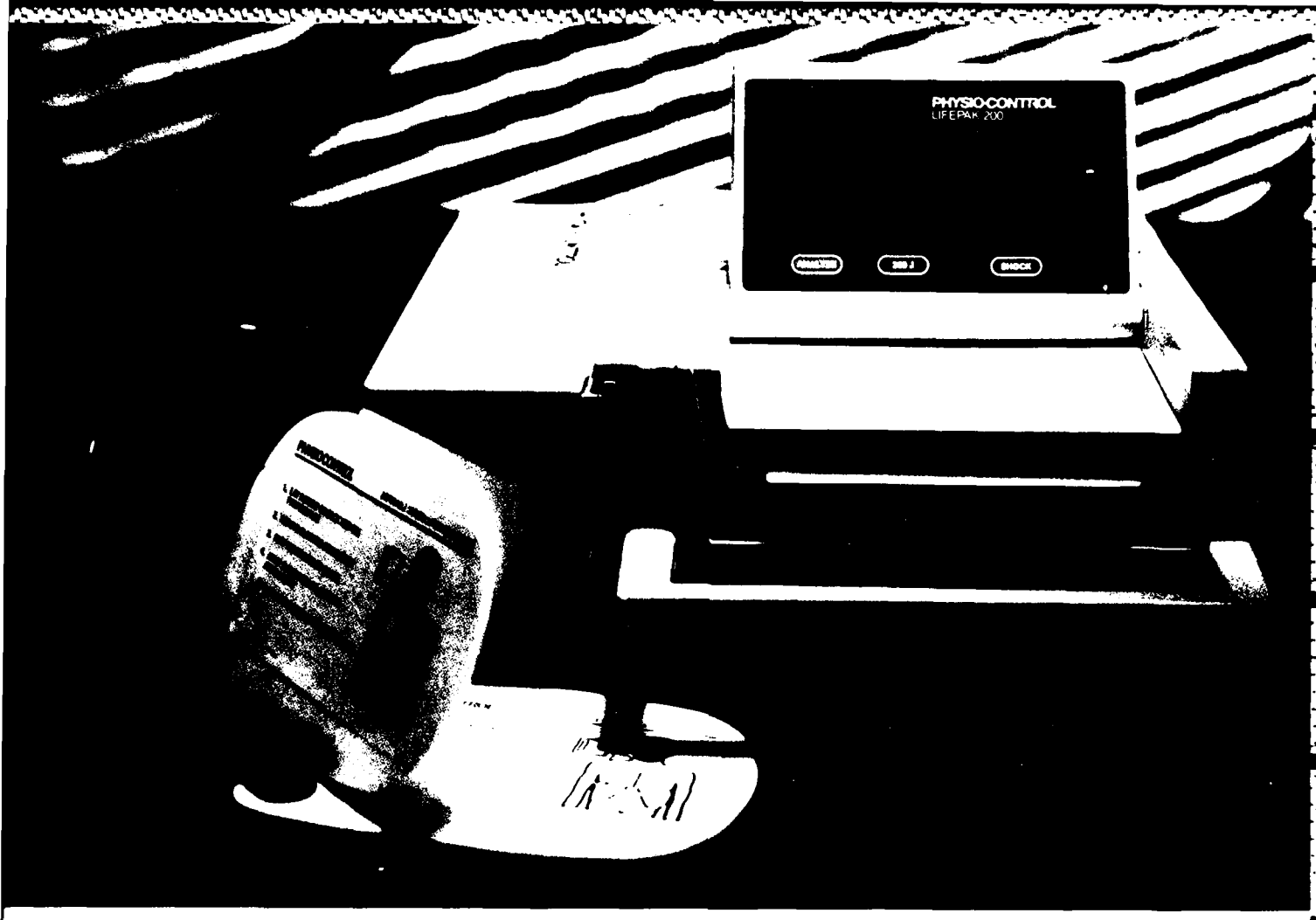
Vials containing 2 gm equivalent of ceftriaxone sodium: Boxes of 10 (NDC 0004-1965-01).

Piggyback bottles containing 2 gm equivalent of ceftriaxone sodium: Boxes of 10 (NDC 0004-1965-03).

Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone sodium: Boxes of 1 (NDC 0004-1971-01). NOT FOR DIRECT ADMINISTRATION.

This product information issued February 1985

ROCHE®
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110



A new generation of emergency responders . . . deserves a new generation of defibrillators.

Physio-Control's new LIFEPAK 200 automatic advisory defibrillator is so safe and simple to operate that a broader range of emergency responders can now be trained to provide on-the-scene defibrillation therapy.

The LIFEPAK 200 defibrillator features a sophisticated Shock Advisory System which performs an ECG analysis so accurate that operator training in rhythm interpretation is unnecessary.

Standard features include an ECG/voice recorder, low maintenance Battery Pak and integral charger. All in a portable, rugged package that weighs less than 15 pounds.

To find out more about this revolutionary new defibrillator, call or write for our brochure.

Physio-Control.
Defining the standard for the next generation of defibrillator/monitors.

Session 3: Brain Resuscitation

The panel on brain resuscitation included discussions on the ischemic neuron and its environment, the initial evaluation of cerebral insult, and clinical maneuvers that can affect recovery. In developing a perspective on resuscitation research, the discussants have raised three issues: our lack of ability to measure physiologic and hemodynamic variables in the central nervous system; the variability of study design; and the reproducibility of results.

Measuring Physiologic Parameters

The first step in transferring basic science knowledge to the clinical setting is the ability to measure the physiologic and hemodynamic variables of the central nervous system, and the ability to adapt such methods of measurement to the clinical setting. Current methods of evaluating the CNS vary, but often are too difficult and too sophisticated to extrapolate from the researcher and his laboratory to the clinician and his laboratory.

For example, cerebral blood flow determination has been accomplished by the microsphere technique, venous outflow determination, carotid blood flow measurement, and thermodilution. Assessing the integrity of the blood-brain barrier, cell function, and neuronal environment depends on biochemical analysis and electron microscopy. Cortical tissue pressures can be measured only in the animal laboratory. Measurement of intracranial pressure is now a fairly routine clinical neurosurgical procedure. Gross structure and function are measured by the electroencephalogram, by computerized axial tomogram and, in a few centers, by nuclear magnetic resonance. The "gold standard" of central nervous system function, however, is measurement of ultimate neurologic recovery, which can be accomplished during properly designed clinical investigation.

Only a few of these determinations are currently adaptable for general investigation. ICP measurement, EEG, CT scan, and measurement of clinical neurological recovery using clinical grading scales. It seems, therefore, that one objective of resuscitation research ought to be to develop clinically useful methods of physiologic and hemodynamic measurement of the central nervous system.

Study Design

Dr Rehncrona's studies demonstrate the importance of the prior metabolic and physiologic state of the experimental animal to the results of resuscitation research. The clinical effectiveness, or lack of effectiveness, of laboratory-determined treatments, such as calcium channel blockers or barbiturates, certainly depends on the as-yet-undetermined prior physiologic parameters of the human subject. Today's "black box" approach to clinical resuscitation research may overlook a subgroup that might well benefit from an otherwise ineffective maneuver.

Study costs and the need for large numbers of animals have led to the use of many species of small animals in investigations. Extrapolation of data to the human model cannot, therefore, be totally accurate. Arrest-resuscitation models must be carefully analyzed before the clinical usefulness of laboratory-evaluated techniques may be assumed. For example, models of total anoxia versus partial or total ischemia produce different results. Laboratory resuscitation techniques, such as open-chest massage, may not be applicable to the clinical setting. Unless such correlations are made, what appears promising in the laboratory may become a clinical disappointment.

Cerebral resuscitation studies are designed variously to determine acute (minutes), subacute (hours), and prolonged (days) neurologic response. The costs and technical difficulties of prolonged laboratory follow-up have led to a predominance of studies designed to look at the acute or subacute response. Few, if any, of these can be extrapolated to the "gold standard" of ultimate neurologic recovery.

Reproducibility of Studies

Just as there are multicenter clinical trials, the use of multilaboratory studies should be considered, to hasten the acquisition of data as well as to determine the suitability of the selected methodology and reproducibility of techniques and results. The multilaboratory approach would help to analyze therapeutic/toxic ratios of agents used, and would help to determine at which point clinical trials are indicated.

Judith E Tintinalli, MD
Department of Emergency Medicine
William Beaumont Hospital
Royal Oak, Michigan

SPECIAL CONTRIBUTION
brain ischemia; glucose; lactic acid; neurologic outcome

Brain Acidosis

Brain tissue acidosis is a result of either an increase in tissue PCO_2 or an accumulation of acids produced by metabolism. Severe hypercapnia (arterial PCO_2 around 300 mm Hg) may cause a fall in tissue pH to around 6.6 without any deterioration of the cerebral energy state or morphologic evidence of irreversible cell damage. In severe ischemia and tissue hypoxia, anaerobic glycolysis leads to lactic acid accumulation. This is aggravated by hyperglycemia and by a (trickling) residual blood flow. Under such circumstances lactate concentration in the tissue may increase to levels above 20 to 25 μmol/g (tissue wet weight), causing a decrease in pH to around 6.0. If lactic acidosis during ischemia or hypoxia reaches these excessive levels, metabolic and functional restitution is severely hampered upon subsequent recirculation and reoxygenation. In these circumstances cell morphology shows signs of irreversible damage. Conversely there is less damage if severe tissue lactic acidosis can be hindered. The deleterious effect of excessive lactic acidosis may be related to an influence on the following: synthesis and degradation of cellular constituents; mitochondrial function; cell volume control; postischemic blood flow; and stimulation of pathologic free radical reactions. Possibilities for therapeutic interventions include the avoidance of hyperglycemia, inhibition of glycolysis, and measures for increasing the buffer capacity of the brain. [Rehncrona S: Brain acidosis. Ann Emerg Med August 1985;14:770-776.]

Stig Rehncrona, MD, PhD
Lund, Sweden

From the Department of Neurosurgery and the Laboratory for Brain Research, University Hospital, Lund, Sweden.

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985.

Address for reprints: Stig Rehncrona, MD, Department of Neurosurgery, 4, E Blocket, University Hospital, S-221-85, Lund, Sweden

INTRODUCTION

Brain cells are relatively well protected from even severe systemic metabolic acid-base disturbances. There are several mechanisms by which this is accomplished. The cells of the brain are surrounded by a buffered extracellular fluid with its own capacity for pH regulation. Brain cells are also separated from the blood by the blood-brain barrier, which has low permeability to ionic compounds like H^+ and HCO_3^-. Because CO_2, like other gas compounds, is freely diffusable, a change in blood PCO_2 is readily transmitted to both extra- and intracellular fluids of the brain. Therefore, much interest in brain acid-base balance originally focused on the effect of respiratory changes, and much of our current knowledge of brain pH regulation emanates from experiments with hypo- and hypercapnia.[1] Brain acid-base chemistry, especially that of the intracellular compartment, has gained renewed attention with recent demonstrations of a relationship between metabolic tissue acidosis and cell damage.

More than 20 years ago Friede and Van Houten[2] related cellular injury in incubated brain tissue slices to the development of metabolic acidosis. They observed that morphologic changes were more severe if oxidative metabolism alone was blocked (with cyanide) than if both glycolysis and cellular respiration were blocked simultaneously. Lindenberg in 1963[3] hypothesized that structural alterations in the hypoxic brain described as "morphotropic necrobiosis" were caused by intracellular acidosis. It was only recently established with in vivo models, however, that severe tissue lactic acidosis limits the possibility for cell survival in brain ischemia.[4-9]

The purpose of this article is to review data on the relationship between severe tissue acidosis and irreversible brain cell damage. In this context, a summary discussion of cerebral pH regulation, which has been thoroughly reviewed elsewhere,[1,10] will be helpful for understanding the acid-base issues

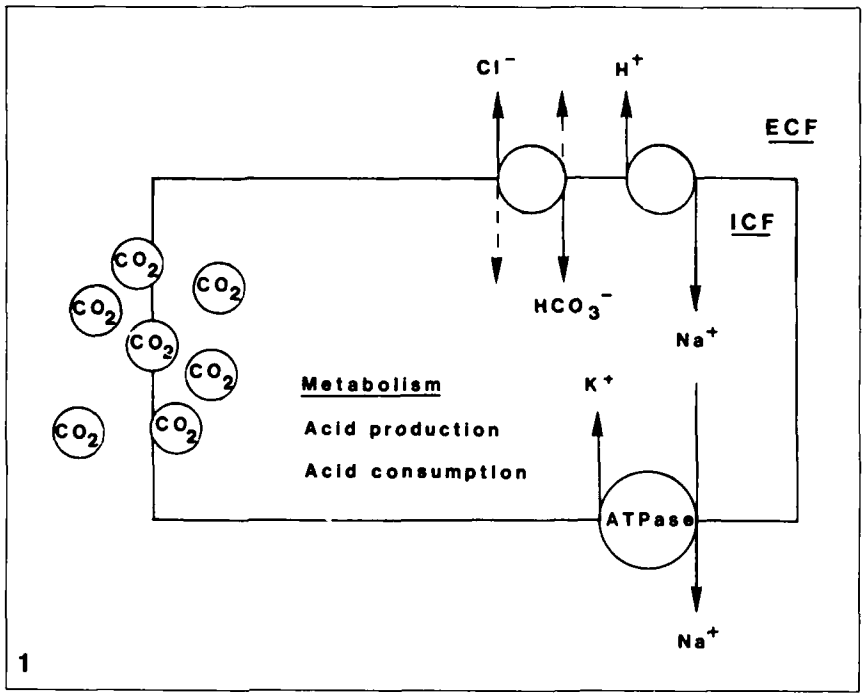


Fig. 1. *Diagram illustrating some mechanisms of importance for intracellular pH regulation in the brain.*

in brain pathophysiology.

CEREBRAL pH REGULATION

The most important mechanisms serving to maintain brain pH homeostasis are physicochemical buffering, production or consumption of metabolic acids, and transmembrane fluxes of H^+ and HCO_3^-. Both extra- and intracellular fluids of the brain contain buffer systems, the most important being bicarbonate-carbonic acid (HCO_3^-/H_2CO_3). In addition, the intracellular fluid contains a number of nonbicarbonate buffers and has a total buffering capacity approaching that of the blood.

A change in intracellular pH homeostasis usually is due either to a change in PCO_2 or to a net increase in metabolic acid production. An increase or decrease in PCO_2, tending to induce respiratory acidosis or alkalosis, can to some extent be compensated for by increased consumption or production of metabolic acids, ie, by an increase or decrease in buffer base (BB) concentration. Conversely an acid load due to the accumulation of metabolic acids may to some extent be compensated for by a decrease in PCO_2 (hyperventilation). However, the capacity of respiratory compensation for a metabolic acid load is rather small. Siesjö[1] demonstrated that an increase of the steady state concentration of lactic acid in intracellular water by 6 μmol/g would require a drop in PCO_2 to 25 mm Hg for pH to remain unchanged.

In addition to physicochemical buffering and metabolic regulation, the intracellular pH depends on transmembrane fluxes of H^+ and HCO_3^- ions. Extrusion of H^+ from the intracellular compartment is thought to occur in exchange for Na^+ through an antiport system. This acid extrusion is energy demanding; the driving force is the Na^+-gradient created by the membrane bound Na^+, K^+-ATPase. HCO_3^- may be transported inside the cell by another antiporter in exchange for chloride anions. The HCO_3^-/Cl^- antiport system, which does not seem to be energy dependent, may be reversed so as to cause a leakage of H^+ back into the cell.[11] A simplified diagram illustrating these important processes for brain intracellular pH regulation is shown (Figure 1).

BRAIN TISSUE ACIDOSIS AND CELL DAMAGE

Intracellular hydrogen ion concentration may increase due to principally two different mechanisms, that is, either by an increase in PCO_2 (hypercapnia) or by increased net production of lactic acid within the cell.

Hypercapnic Acidosis

In clinical medicine hypercapnia often is recognized in situations of respiratory insufficiency, and therefore it is frequently associated with hypoxemia. This creates a complex situation at the cellular level. Experimental data on pure hypercapnia, obtained by ventilating animals with gas mixtures containing a high CO_2 concentration at normoxia, have shown that brain intracellular pH drops from a normal value of 7.04 to 6.90 at an arterial PCO_2 of 90 mm Hg, and to around 6.65 at PCO_2 in the range of 250 to 300 mm Hg.[12] At this extremely high (in fact, anesthetic) CO_2 tension, there is no pertubation of the cerebral energy state even during 45 minutes of CO_2 exposure.[13] Furthermore, such hypercapnic exposure induced scarcely any irreversible cell changes as evaluated by light- and electron-microscopy.[14] Therefore, it seems reasonable to conclude that the brain can resist this degree of acidosis (pH = 6.65) without gross or irreversible damage if there is no concomitant deterioration of the cerebral energy state.

Ischemic Acidosis

In severe ischemia (and tissue hypoxia) oxygen delivery to brain cells is insufficient for normal energy production, and acid-base homeostasis is threatened by the accumulation of acid equivalents (metabolic acidosis). This situation differs from hypercapnic acidosis by being associated with a perturbation of the energy state. Glycolysis proceeds (at an increased rate) in the absence of oxygen, and the metabolism of glycolytic substrates (glucose and glycogen) terminates before pyruvate oxidation. Due to the intracellular redox shift with an increased $NADH/NAD^+$ ratio, the lactate dehydrogenase (LDH) equilibrium is strongly shifted to the right, resulting in the production and accumulation of lactic acid:

$$\text{pyruvate} + NADH + (H^+) \underset{}{\overset{\text{LDH}}{\rightleftharpoons}} \text{Lactate} + NAD^+$$

Glycolytic metabolism supplies the cell with minor amounts of energy in

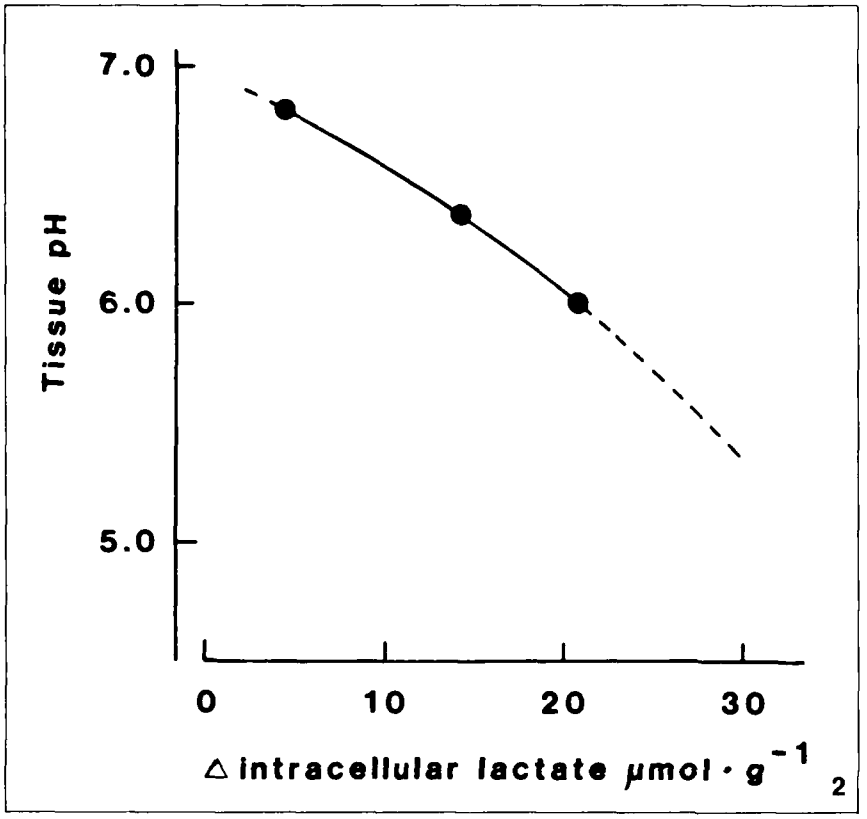


Fig. 2. *Brain tissue pH as a function of the change in tissue lactate concentration during ischemia. (Based on values from Ljunggren B, Norberg K, Siesjö BK: Influence of tissue acidosis upon restitution of brain energy metabolism following total ischemia. Brain Res 1974;77:173. With courtesy from the authors.)*

the form of ATP (about 5% of the energy yield from oxidative metabolism) at the expense of pH homeostasis, ie, a fall in buffer base concentration and in pH.

Evidence for a deleterious effect of increased lactic acid accumulation during ischemia in vivo was first presented by Myers and associates,[4] who found that glucose pretreatment of animals worsened the outcome of reversible ischemic-hypoxic insults. Siemkowicz and Hansen[5,15] reasoned that because brain hyperglycemia prolonged the time between induction of complete ischemia and membrane failure (defined as the point at which massive K^+ efflux to the extracellular fluid occurs), preischemic glucose loading might have a protective effect due to additional energy contribution. Quite to the contrary, using a model of ten minutes of complete ischemia with subsequent recirculation, they found a considerably better neurologic restitution in normoglycemic than in hyperglycemic animals.[5]

The hypothesis of a detrimental effect of severe tissue lactic acidosis was further corroborated by findings that a trickling blood flow during ischemia may be more harmful than a total interruption of the cerebral circulation.[16-18] Because interruption of blood flow excludes any exogenous substrate supply, the maximal level to which lactate accumulates during complete ischemia is limited by the size of the endogenous stores of glucose and glycogen in the tissue.[19] When ischemia is incomplete, which often is more relevant to clinical medicine, the situation is different, and lactate accumulation may be exaggerated. Thus a decrease of the cerebral blood flow to levels below those critical for oxidative metabolism but which still allow some glucose supply for continued glycolysis may cause an ever-increasing lactate concentration.

This issue was examined using a model of reversible incomplete ischemia (CBF below 5% of normal) in rats fasted for 24 hours and treated either with a saline or a glucose solution just prior to ischemia.[7,8] The results were clear. In animals with blood glucose concentrations in the lower normal range, brain lactate concentration increased from a normal value of 1.0 μmol/g to about 15 μmol/g during 30 minutes of ischemia. Upon recirculation, these animals showed considerable recovery of the cerebral energy state, and return of spontaneous electrocortical activity as well as of the somatosensory evoked response (SER).[7] Light- and electronmicroscopy revealed only minimal reversible cell changes at the end of ischemia and during a 90-minute subsequent recirculation period.[8] In hyperglycemic animals, tissue lactate concentration increased to above 30 μmol/g, and upon recirculation there was no recovery of cerebral energy metabolism or of any of the neurophysiologic variables. In these animals histopathologic evaluation showed widespread brain cell damage at five minutes postischemia and irreversible changes after 90 minutes of recirculation. Similarly, the metabolic recovery after 30 minutes of complete ischemia was shown to be worse when ischemic tissue lactic acidosis was aggravated by preischemic tissue hyperglycemia. Hyperglycemia caused lactate concentration to increase from 12 μmol/g with normoglycemic ischemia to about 25 μmol/g. Taken together these results indicate that a concentration of lactate above 20 to 25 μmol/g in the ischemic brain is deleterious to metabolic recovery and may induce irreversible damage. Conversely the brain may resist even prolonged periods of ischemia without persistent energy failure or structural damage, provided that lactic acidosis does not reach excessive levels, ie, levels above 20 μmol/g.

Neuronal function is certainly more sensitive than the metabolic machinery. Interestingly the immediate recovery of neuronal function also seems dependent on the level of ischemic tissue lactic acidosis, even if levels critical for metabolic recovery are not reached. Thus the postischemic restitution of neurophysiologic variables was found to be inversely proportional to ischemic lactate accumulation (in the range 10 to 20 μmol/g), even when the recovery of cerebral energy state

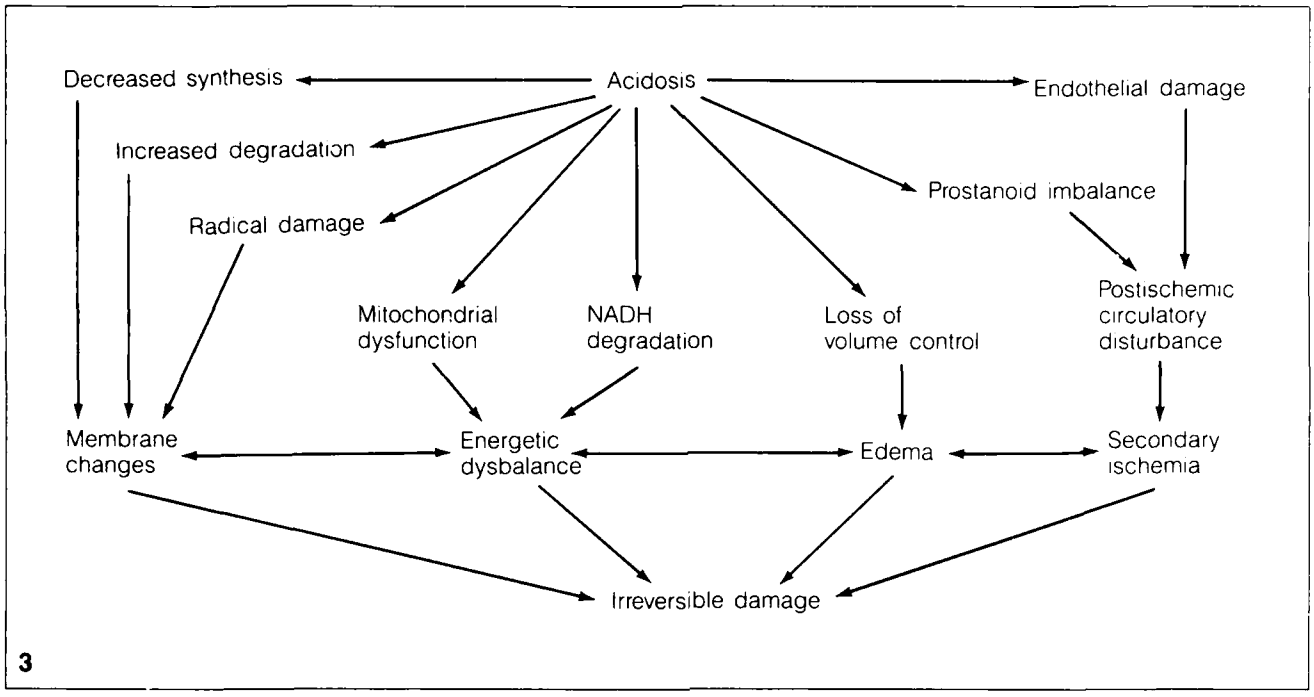


Fig. 3. *Proposed influence of severe acidosis on mechanisms that may cause irreversible brain cell damage.*

was complete.[20] Therefore, there may be some difference in critical levels of ischemic tissue lactic acidosis for metabolic and for functional recovery.

Hypoxemic Acidosis

Arterial hypoxia induces a compensatory increase in the cerebral blood flow that protects the tissue from a major fall in oxygen availability. Experiments with artificially ventilated animals have shown that the arterial oxygen tension (PaO_2) may be decreased to 25 mm Hg in uncomplicated hypoxia without any perturbation of the energy state or increase in tissue lactate concentration to above 8 to 10 μmol/g. In clinical cases, however, severe hypoxia is often complicated by factors that counteract the homeostatic effect of cerebral vasodilatation. Such factors include a drop in blood pressure, hypoxic heart failure, and arteriosclerotic disease that may curtail the compensatory hyperemia. Such clinical situations are mimicked experimentally by severe hypoxia induced in rats after clamping of one carotid artery. From a metabolic point of view this preparation has similarities with incomplete ischemia. Thus oxygen delivery to the tissue ipsilateral to the occluded carotid artery may be decreased to levels insufficient for oxidative metabolism; however, CBF still is near normal,[21] and the tissue is supplied with glucose. In physiologically well-controlled experiments with artificially ventilated animals, results with this preparation have shown that lactate accumulates in parallel to a deterioration of the cerebral energy state, and may reach excessive levels (20 to 50 μmol/g) only in the ipsilateral hemisphere.[21] Perfusion fixation of the brain in the reoxygenation phase demonstrates that severe morphologic alterations develop only on the occluded side.[22] Because decreased lactate production during the hypoxic insult improves recovery, it seems likely that severe lactic acidosis is a pathogenetic factor for brain damage also in hypoxic situations.[23]

Other Conditions

It is theoretically reasonable that enzymatic defects and/or mitochondrial dysfunction could cause an accumulation of metabolic acids with intracellular acidosis in the brain. Except for thiamine deficiency, however, few data are available on the possible relationship between acidosis and neuronal damage in such diseases. Thiamine (vitamin B_1), in the form of pyrophosphate, is a cofactor for pyruvate dehydrogenase, and thiamine deficiency may lead to regional accumulation of lactate in the brain.[24] Data on brain pH in thiamine-deficient rats (measured autoradiographically using the ^{14}C-DMO technique) demonstrate tissue acidosis with tissue pH below 6.50 in certain regions.[25] The regions with the most severe acidosis coincide with those known to be most vulnerable in this disease, and it was suggested that brain acidosis may be in part responsible for the injury.

MOLECULAR MECHANISMS FOR ACIDOTIC DAMAGE

Certainly the final outcome of brain ischemia or hypoxia depends on several factors that may operate during the insult period and/or in the postinsult phase. Moreover such factors may influence each other to create rather complex mechanisms. Nevertheless severe tissue lactic acidosis now seems to be a major detrimental factor. Although other effects of lactate accumulation (and of hyperglycemia) should be considered as well, the most direct pathophysiologic explanation for the cell injury is a fall in intra- and extracellular pH. Extracellular pH has

been measured with microelectrodes during complete ischemia in normo- and hyperglycemic rats. In these experiments pH falls from a normal value of 7.2 to 6.5 in normoglycemia and 6.1 in hyperglycemia.[26] Data on the relationship between lactate accumulation and tissue pH (Figure 2) indicate that intracellular pH may be decreased to below 6.0 if lactate accumulates above those levels critical for cellular viability (ie, 20 to 25 μmol/g).[4,6] Although the lactate-pH relationship given in Figure 2 is derived from experiments with complete ischemia with a constant total CO_2 content in the tissue, it is likely that the same relationship holds during severe incomplete ischemia.[2] The residual CBF in severe incomplete ischemia is extremely low, and it can be assumed that only minute amounts of CO_2 will escape from the tissue. Moreover, because transmembrane fluxes of H^+ and HCO_3^- are slow, these ion exchange systems cannot be expected to ameliorate cellular acidosis during severe incomplete ischemia.

The exact molecular mechanisms by which the increase in intracellular hydrogen ion activity leads to cell damage remain a matter of speculation. This is partly due to the fact that changes in pH outside the close physiologic range must influence a great many enzyme systems and biochemical reactions, including those for synthesis and degradation of cell constituents. Thus in addition to association with deleterious effects on cell structure and energy metabolism, a large acid load may well influence specialized neuronal functions such as the metabolism of transmitter substances. Some of the current concepts of the development of ischemic and hypoxic tissue injury (Figure 3) deserve special attention in relation to tissue acidosis.

Mitochondrial Dysfunction

Brain mitochondria and mitochondria from several other tissues are sensitive to changes in pH. Exposure of isolated mitochondria to acidosis causes an inhibition of ADP-stimulated (state 3) respiratory activity. At pH of 6.0 and below ATP production ceases.[27] Normalization of pH after five minutes of exposure to this low pH range results in incomplete recovery of respiratory activity.[27] These results with in vitro acidosis corroborate earlier in vivo results showing persistent mitochondrial dysfunction upon recirculation following 30 minutes of severe incomplete ischemia resulting in deep tissue acidosis.[18] Furthermore, mitochondrial Ca^{2+} sequestering capacity is dependent on the energy requiring chemiosmotic gradient of H^+ across the mitochondrial membrane, and may therefore be disturbed by an alteration of the intracellular pH homeostasis.[28] Resynthesis of ATP to restore energy balance after ischemia requires NADH for reoxidation by the electron transport chain. Welsh and associates[29] have shown that the size of the total NA pool (NADH + NAD^+) may decrease significantly during ischemia, and suggested that this may limit ATP regeneration. Because tissue lactic acidosis in their model is excessive (with tissue lactate concentrations approaching 40 μmol/g) it was suggested that the decrease in NAD pool size was at least partly due to an acid-catalyzed destruction of NADH[30] accelerated by acidosis.

Postischemic CBF Disturbances

Restoration of an adequate blood supply and tissue oxygenation is a prerequisite for neurologic recovery after ischemia-hypoxia. Although a primarily deficient recirculation (no-reflow) may hamper recovery,[31] the postischemic cerebral blood flow usually is characterized by initial hyperemia followed by secondary hypoperfusion.[32] Severe, delayed hypoperfusion may induce a new ischemic situation with aggravation of tissue damage. Ischemic tissue acidosis may influence the postischemic circulation in several ways. From experimental data it seems clear that a late deterioration of cerebral blood flow is more intense if the preceding ischemia is complicated by excessive tissue acidosis.[33] This observation may be explained by progressive endothelial swelling with a decrease of capillary luminal diameter.[34] Ischemia leads to an increase in tissue content of free fatty acids, notably of free arachidonic acid, which is rapidly metabolized to prostaglandins in the early recirculation phase.[35,36] Because prostacycline, the major vasodilator and platelet antiaggregatory prostaglandin, is extremely labile at an acid pH,[37] it may be that acidosis disturbs the balance between vasoactive prostaglandins with resulting predominance of vasoconstrictor effects in the postischemic phase.

It should be noted that tissue acidosis continues for some time after restoration of perfusion but is then succeeded by alkalosis, the degree of which may depend on the degree of the preceding acid load[38] (compare reference 25). A possible explanation of this alkalotic shift is reoxidation of accumulated acid equivalents together with active H^+ efflux. Interestingly these pH shifts coincide with hyperemia and hypoperfusion in the postischemic phase, but the exact relationship, if any, is obscure.

Free Radical Mechanisms

Although their role is not yet clear, free radical mechanisms causing lipid peroxidation and thereby aggravating cell damage in ischemia followed by reoxygenation also should be considered. It is generally believed that pathologic free radical mechanisms in biological systems are initiated by hydroxyl radicals ($OH^\bullet$) formed from superoxide (O_2^-) and hydrogen peroxide (H_2O_2) in the Haber-Weiss reaction catalyzed by free iron.[39] Studies on brain homogenates incubated with oxygen have shown that the rate of peroxidation depends on the free iron concentration.[40] However, the tissue iron is normally bound to hemoproteins, ferritin and transferrin and is therefore not available for participation as a catalyst in these reactions. Because lipid peroxidation (at least in vitro) is enhanced by a reduction in pH, an effect that may be due to decompartmentalization of iron,[41,42] acidosis in vivo may contribute to peroxidative damage.

Tissue Edema

In animals with a high degree of lactic acidosis during ischemia, the histopathologic features of postischemic brain damage include prominent cell edema, notably with swelling of astrocytes.[5] Because an increase in brain lactate concentration to 20 μmol/g would cause a 6% increase in osmolality, the osmotic effect of accumulated lactate may have some influence on cell volume. Siesjo[43] recently has proposed another mechanism by which the increase in intracellular H^+ concentration may be the triggering factor leading to edema formation. According to this hypothesis, H^+ ions are pumped out of the cell in exchange for Na^+, the rate of ion ex-

change being proportional to H^+. Thus intracellular acidosis would enhance influx of Na^+. The consequent increase in extracellular H^+ concentration will cause a fall in interstitial HCO_3^- by conversion to CO_2. CO_2 is removed by the restored blood flow, but the reduced extracellular HCO_3^- will trigger an efflux of intracellular HCO_3^- in exchange for Cl^- (Figure 1). These ionic shifts would increase net transport of both Na^+ and Cl^- into the cell, along with water, causing an increase of the intracellular fluid volume and cell swelling.

CLINICAL IMPLICATIONS

Two retrospective clinical studies lend support to the idea that ischemic tissue acidosis has clinical significance. Poor neurologic recovery in patients resuscitated after out-of-hospital cardiac arrest was found to be associated with a high blood glucose level on admission.[11] A similar study on the outcome after ischemic stroke showed increased morbidity and mortality in diabetic patients with hyperglycemia at admission.[12] These early clinical observations are not fully conclusive and further clinical studies are needed. Nevertheless the experimental data we have reviewed strongly suggest that therapeutic measures to prevent or ameliorate tissue acidosis in clinical cases with a critically reduced cerebral perfusion pressure might be useful. Some possibilities for therapeutic intervention are discussed below.

The development of brain tissue lactic acidosis in ischemia depends on several factors, the most important of which are the following: 1) the rate of the residual blood flow, 2) the ischemic time period, 3) the blood glucose concentration, and 4) the glycolytic rate. At least the last two variables are therapeutically accessible. Thus it is suggested that measures should be taken to prevent hyperglycemia from occurring, eg, by avoiding an increase in blood glucose by sympato-adrenal activation related to stress, by avoiding infusions with solutions containing an unnecessarily high concentration of glucose, and possibly by insulin treatment. Because an increase in PCO_2 not only tends to decrease pH but also causes an increased brain glucose/blood glucose ratio,[7] hypercapnia should be avoided.

A second possibility may be to decrease lactate production by inhibition of glycolytic rate. This can be achieved by barbiturate treatment[10] or by hypothermia.[13] Certainly such therapy does not prevent lactic acidosis during ischemia, but at least it will delay the time period for lactic acid concentration to reach critical levels. The effectiveness of such therapy in clinical cardiac arrest, quite naturally, is limited by the practical restriction to postresuscitation application after the maximal ischemic insult and lactic acid accumulation has occurred.

The third possibility to be discussed remains hypothetical and concerns measures for increasing the buffer capacity of the brain. Because buffer anions (such as HCO_3^- and Tris[+]) penetrate the blood brain barrier only at very slow rates, administration of such buffers through the blood seems to be quite inefficient. Intrathecal administration of base, thereby bypassing the blood brain barrier, could at least theoretically ameliorate an acid load, but it involves a risk for overcorrection in the reoxygenation phase.[11] This could result in a severe brain alkalosis, the pathophysiologic influence of which we know little. In addition, this administration route may imply that only cells in close proximity to CSF are affected. Although a pharmacologic approach to increase intracellular buffer capacity seems to be afflicted with many obstacles, it still may be an important method of future treatment. Thus a further search for suitable ways to increase the intracellular buffer capacity of the brain is in order.

REFERENCES

1. Siesjo BK: *Brain Energy Metabolism*. Chichester, New York, John Wiley & Sons, 1978.

2. Friede RL, Van Houten WH: Relations between post mortem alterations and glycolytic metabolism in the brain. *Exp Neurol* 1961;4:197-204.

3. Lindenberg R: Patterns of CNS vulnerability in acute hypoxaemia, including anaesthesia accidents, in Schade JP, McMenemey WH (eds): *Selective Vulnerability of the Brain in Hypoxaemia*. Philadelphia, FA Davis Co, 1963, pp 189-210.

4. Myers RE: A unitary theory of causation of anoxic and hypoxic brain pathology, in Fahn S, Davis JN, Rowland LP (eds): *Advances in Neurology*, vol 26: *Cerebral Hypoxia and Its Consequences*. New York, Raven Press, 1979, pp 195-213.

5. Siemkowicz E, Hansen A: Clinical restitution following cerebral ischemia in hypo- normo- and hyperglycemic rats. *Acta Neurol Scand* 1978;58:1-8.

6. Rehncrona S, Rosen I, Siesjo BK: Excessive cellular acidosis: An important mechanism of neuronal damage in the brain? *Acta Physiol Scand* 1980, 110:435-437.

7. Rehncrona S, Rosen I, Siesjo BK: Brain lactic acidosis and ischemic cell damage: I. Biochemistry and neurophysiology. *J Cereb Blood Flow Metab* 1981;1:297-311.

8. Kalimo H, Rehncrona S, Soderfeldt B, et al: Brain lactic acidosis and ischemic cell damage: 2. Histopathology. *J Cereb Blood Flow Metab* 1981;1:313-327.

9. Pulsinelli WA, Waldman S, Rawlinson D, et al: Moderate hyperglycemia augments ischemic brain damage: A neuropathologic study in the rat. *Neurology* 1982;32:1239-1246.

10. Roos A, Boron WF: Intracellular pH. *Physiol Rev* 1981;61:296-434.

11. Siesjo BK: Administration of base via the CSF route: A clinically useful treatment of cerebral acidosis? *Intensive & Critical Care Digest* 1984;3:5-9.

12. Siesjo BK, Folbergrova J, MacMillan V: The effect of hypercapnia upon intracellular pH in the brain, evaluated by the bicarbonate-carbonic acid method and from the creatine phosphokinase equilibrium. *J Neurochem* 1972;19:2483-2495.

13. Folbergrova J, MacMillan V, Siesjö BK: The effect of moderate and marked hypercapnia upon the energy state and upon the cytoplasmic NADH/NAD^+ ratio of the rat brain. *J Neurochem* 1972;19:2497-2505.

14. Paljärvi L, Söderfeldt B, Kalimo H, et al: The brain in extreme respiratory acidosis. A light- and electron-microscopic study in the rat. *Acta Neuropathol (Berl)* 1982;58:87-94.

15. Hansen AJ: The extracellular potassium concentration in brain cortex following ischemia in hypo- and hyperglycemic rats. *Acta Physiol Scand* 1978;102:324-329.

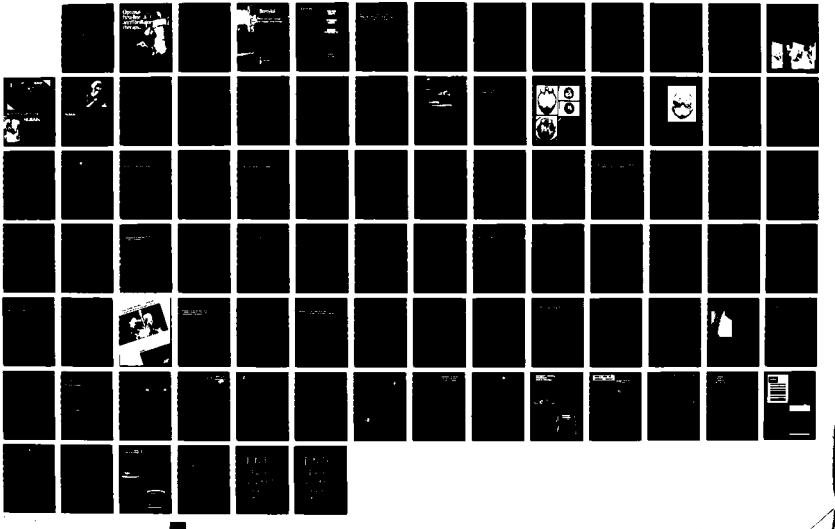
16. Hossmann K-A, Kleihues P: Reversibility of ischemic brain damage. *Arch Neurol* 1973;29:375-384.

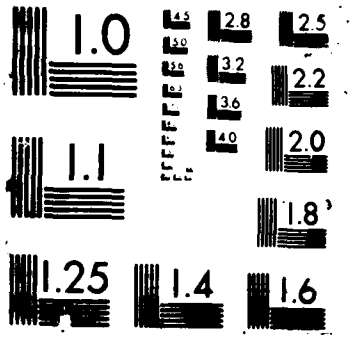
17. Nordstrom C-H, Rehncrona S, Siesjo BK: Effects of phenobarbital in cerebral ischemia. Part 2: Restitution of cerebral energy state, as well as of glycolytic metabolites, citric acid cycle intermediates and associated amino acids after graded incomplete ischemia. [illegible] 335-343.

18. Rehncrona S, M[illegible] covery of brain [illegible] the rat after [illegible] [illegible]

AD-A187 110 PROCEEDINGS OF THE UAEM/IRIEM RESEARCH SYMPOSIUM ON RESUSCITATION (1985)(U) UNIVERSITY ASSOCIATION FOR EMERGENCY MEDICINE LANSING MI AUG 85 DAMD17-85-G-5007 2/2

UNCLASSIFIED F/G 6/5 NL




1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0

Optimal first-line antifibrillator therapy...

19. Ljunggren B, Norberg K, Siesjö BK: Influence of tissue acidosis upon restitution of brain energy metabolism following total ischemia. *Brain Res* 1974;77:173-186.

20. Rehncrona S, Rosén I, Smith M-L: The effect of different degrees of brain ischemia upon the short term recovery of neurophysiologic and metabolic variables. *Exp Neurol* 1985;87:458-473.

21. Salford LG, Siesjö BK: The influence of arterial hypoxia and unilateral carotid artery occlusion upon regional blood flow and metabolism in the rat brain. *Acta Physiol Scand* 1974;92:130-141.

22. Salford LG, Plum F, Brierley JB: Graded hypoxia-oligemia in rat brain. II. Neuropathological alterations and their implications. *Arch Neurol* 1973;29: 234-238.

23. Gardiner M, Smith ML, Kagström E, et al: Influence of blood glucose concentration on brain lactate accumulation during severe hypoxia and subsequent recovery of brain energy metabolism. *J Cereb Blood Flow Metab* 1982;2:429-438.

24. McCandless DW: Energy metabolism in the lateral vestibular nucleus in pyrithiamine-included thiamine deficiency, in Sable HZ, Gubler CJ (eds): *Thiamine: Twenty Years of Progress. Ann NY Acad Sci* 1982;378:355-364.

25. Hakim AM: The induction and reversibility of cerebral acidosis in thiamine deficiency. *Ann Neurol* 1984;16:673-679.

26. Siemkowicz E, Hansen AJ: Brain extracellular ion composition and EEG activity following 10 minutes ischemia in normo- and hyperglycemic rats. *Stroke* 1981;12:236-240.

27. Hillered L, Ernster L, Siesjö BK: Influence of *in vitro* lactic acidosis and hypercapnia on respiratory activity of isolated rat brain mitochondria. *J Cereb Blood Flow Metab* 1984;4:430-437.

28. Fiskum G: Involvement of mitochondria in ischemic cell injury and in regulation of intracellular calcium. *Am J Emerg Med* 1983;2:147-153.

29. Welsh FA, O'Connor MJ, Marcy VR, et al: Factors limiting regeneration of ATP following temporary ischemia in rat brain. *Stroke* 1982;13:234-242.

30. Lowry OH, Passonneau JV, Rock MK: The stability of the pyridine nucleotides. *J Biol Chem* 1961;236:2756-2759.

31. Ames A III, Wright RL, Kowada M, et al: Cerebral ischemia. II: The no-reflow phenomenon. *Am J Pathol* 1968;52: 437-453.

32. Hossmann KA, Lechtape-Grüter H, Hosmann V: The role of cerebral blood flow for the recovery of the brain after prolonged ischemia. *Z Neurol* 1973;204:281-299.

33. Kagström E, Smith M-L, Siesjo BK: Recirculation in the rat brain following incomplete ischemia. *J Cereb Blood Flow Metab* 1983;3:183-192.

34. Paljärvi L, Rehncrona S, Soderfeldt B, et al: Brain lactic acidosis and ischemic cell damage: Quantitative ultrastructural changes in capillaries of rat cerebral cortex. *Acta Neuropathol [Berl]* 1983; 60:232-240.

35. Rehncrona S, Westerberg E, Akesson B, et al: Brain cortical fatty acids and phospholipids during and following complete and severe incomplete ischemia. *J Neurochem* 1982;38:84-93.

36. Gaudet RJ, Levine L: Transient cerebral ischemia and prostaglandins. *Biochem Biophys Res Commun* 1979; 86:893-901.

37. Cho MJ, Allan MA: Clinical stability of prostacyclin (PGI_2) in aqueous solution. *Prostaglandins* 1978;15:943-954.

38. Mabe H, Blomqvist P, Siesjö BK: Intracellular pH in the brain following transient ischemia *J Cereb Blood Flow Metab* 1983;3:109-114

39. Halliwell B, Gutteridge JMC: Oxygen toxicity, oxygen radicals, transition metals and disease. *Biochem J* 1984;219:1-14.

40. Rehncrona S, Smith DS, Akesson B, et al: Peroxidative changes in brain cortical fatty acids and phospholipids, as characterized during Fe^{2+}- and ascorbic acid-stimulated lipid peroxidation *in vitro* *J Neurochem* 1980;34:1630-1638.

41. Barber AA, Bernheim F: Lipid peroxidation: Its measurement, occurrence, and significance in animal tissues. *Adv Gerontol Res* 1967;2:355-403.

42. Siesjo BK, Bendek G, Koide T, et al: Influence of acidosis on lipid peroxidation in brain tissues *in vitro* *J Cereb Blood Flow Metab* 1985;5:253-258.

43. Siesjo BK: Membrane events leading to glial swelling and brain edema, in *Progress in Brain Research*, vol 63, to be published by Springer Verlag, West Germany, 1985

44. Longstreth WT Jr, Inui TS: High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. *Ann Neurol* 1984;15:59-63.

45. Pulsinelli WA, Lewy DE, Sigsbee B, et al: Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. *Am J Med* 1983;74:540-544.

46. Anderson RE, Sundt TM Jr: Brain pH in focal cerebral ischemia and the protective effects of barbiturate anesthesia. *J Cereb Blood Flow Metab* 1983;3:493-497.

47. Thorn W, Scholl H, Pfleiderer G, et al: Metabolic processes in the brain at normal and reduced temperatures and under anoxic and ischemic conditions. *J Neurochem* 1958;2:150-165.

Bretylol®
(bretylium tosylate)

When you give enough, soon enough, long enough.

Give enough Bretylol is most often successful at higher doses. One clinical study found that 300 to 600 mg were generally required in VF.[1] In fact, failure can usually be related to an inadequate dose.[1] In VF, Bretylol should be administered 5 mg/kg by rapid IV bolus, and then 10 mg/kg repeated as necessary.

Soon enough Bretylol is most successful when started early. Early administration, within 15 minutes or less, has been associated with increased survival in countershock-resistant VF patients.[2] Unlike lidocaine and procainamide, Bretylol *significantly* increases the VF threshold and decreases the defibrillation threshold.[3,4] So it is a logical first choice for use after electric countershock, epinephrine, and sodium bicarbonate.

Long enough Bretylol can most successfully prevent VF in post-MI patients when treatment is maintained. In two studies, VF was prevented in nearly all patients who received maintenance doses of Bretylol following MI.[1,5] In patients at risk of ventricular fibrillation, Bretylol should be given by continuous IV drip at a dosage of 1-2 mg/min. Some degree of hypotension is present in approximately 50% of the patients treated and is usually controlled with fluid replacement alone.

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

References: 1. Day HW, Bacaner M. Use of bretylium tosylate in the management of acute myocardial infarction. *Am J Cardiol 27*:177-189, 1971. **2.** Harrison EE, Amey BD. The use of bretylium in pre-hospital ventricular fibrillation. *Am J Emergency Med 1*:1-6, 1983. **3.** Bacaner MB. Quantitative comparison of bretylium with other antifibrillatory drugs. *Am J Cardiol 21*(4):504-512, 1968. **4.** Babbs CF. Evaluation of ventricular defibrillation threshold in dogs by antiarrhythmic drugs. *Am Heart J 98*(3):345-350, 1979. **5.** Castle L. Symposium on the management of ventricular dysrhythmias. *Am J Cardiol 54*(2):26A-33A, 1984.

Please see brief summary of prescribing information on following page

Bretylol® (bretylium tosylate)

Success is a matter of milligrams, minutes, and maintenance.

American Critical Care

American Hospital Supply Corporation

SPECIAL CONTRIBUTION
brain ischemia; deferoxamine; iron;
lipid peroxidation; oxygen radicals; resuscitation

Role of Iron Ions in the Genesis of Reperfusion Injury Following Successful Cardiopulmonary Resuscitation: Preliminary Data and a Biochemical Hypothesis

Presented is a rationale for use of a new class of drugs, the iron chelating agents, in advanced cardiac life support (ACLS) to prevent late deaths and brain damage following successful cardiopulmonary resuscitation. The relevant biochemical hypothesis states that free iron ions, liberated from bound intracellular stores during ischemia, catalyze initiation of free radical mediated reactions that propagate through membrane lipids and proteins. Progressive ultrastructural damage may result, ultimately causing deterioration of function and death. Chelation of intracellular iron by deferoxamine, a commercially available drug that distributes to the intracellular space and has a great affinity for iron ions, may prevent such reactions. A hypothesis concerning relevant pathological chemistry is developed in detail. [Babbs CF: Role of iron in the genesis of reperfusion injury following successful cardiopulmonary resuscitation: Preliminary data and a biochemical hypothesis. Ann Emerg Med August 1985;14:777-783.]

Charles F Babbs, MD, PhD
West Lafayette, Indiana

From the Biomedical Engineering Center, Purdue University, West Lafayette, Indiana

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985

This research was supported in part by Grant HL-29398 from the National Heart, Lung, and Blood Institute, US Public Health Service. Dr Babbs was supported by Research Career Development Award HL-00587, National Heart, Lung, and Blood Institute, US Public Health Service.

Address for reprints: Charles F. Babbs, MD, PhD, Biomedical Engineering Center, Potter Building, Purdue University, West Lafayette, Indiana 47907

Introduction

During the past few years, evidence for a remarkable concept about the pathophysiology of cardiac arrest and resuscitation has begun to accumulate; namely, that significant tissue damage resulting from cardiac arrest and resuscitation occurs not only during the period of circulatory arrest, but also during the period of reperfusion — ie, during the first hours after successful CPR and restoration of spontaneous circulation.[1,2] Indeed, a relatively large proportion of the total injury seen after 5- to 15-minute periods of circulatory arrest may actually develop during the reperfusion phase.

Several factors now are thought to contribute to continuing tissue injury after reperfusion. These include the no-reflow phenomenon of Ames,[3] in which cerebral vascular resistance rises during reperfusion after ischemic-anoxia, thereby selectively decreasing perfusion to areas of the brain; continued calcium influx through cell membranes damaged during ischemic-anoxia, leading to intracellular calcium intoxication during reperfusion in brain and heart;[4-6] and production of oxidative free radicals causing progressive lipid peroxidation in cell membrane systems, leading to cellular dysfunction, especially in the lipid-rich brain.[1,2,7,8]

If irreversible damage to the brain and other organs by such mechanisms does occur during the period of reperfusion, rather than during the period of ischemia-anoxia, then the corresponding pathophysiologic entity, reperfusion injury, may be treatable as part of advanced cardiac life support (ACLS) protocols. Clinical studies have shown that significant central nervous system damage is involved in as many as 59% of inhospital deaths following successful cardiac resuscitation.[9] Severe cardiac dysfunction is reported in 31% of resuscitated patients.[10] To the extent that such damage is generated during the reperfusion period, it is, in principle, preventable by appropriate treatment, either as part of ACLS protocols or as part of postresuscitation intensive care.

Very recently, two independent, preliminary experiments in our laboratory have shown a doubling of the probability of long-term survival of intact animals given the iron chelator deferoxamine (50 mg/kg) after six to ten minutes of total circulatory arrest and CPR (Table).[11,12] In these preliminary studies, cardiac arrest was induced by injection of cold 1% KCl into the left ventricles of ketamine-anesthetized rats pretreated with succinylcholine and

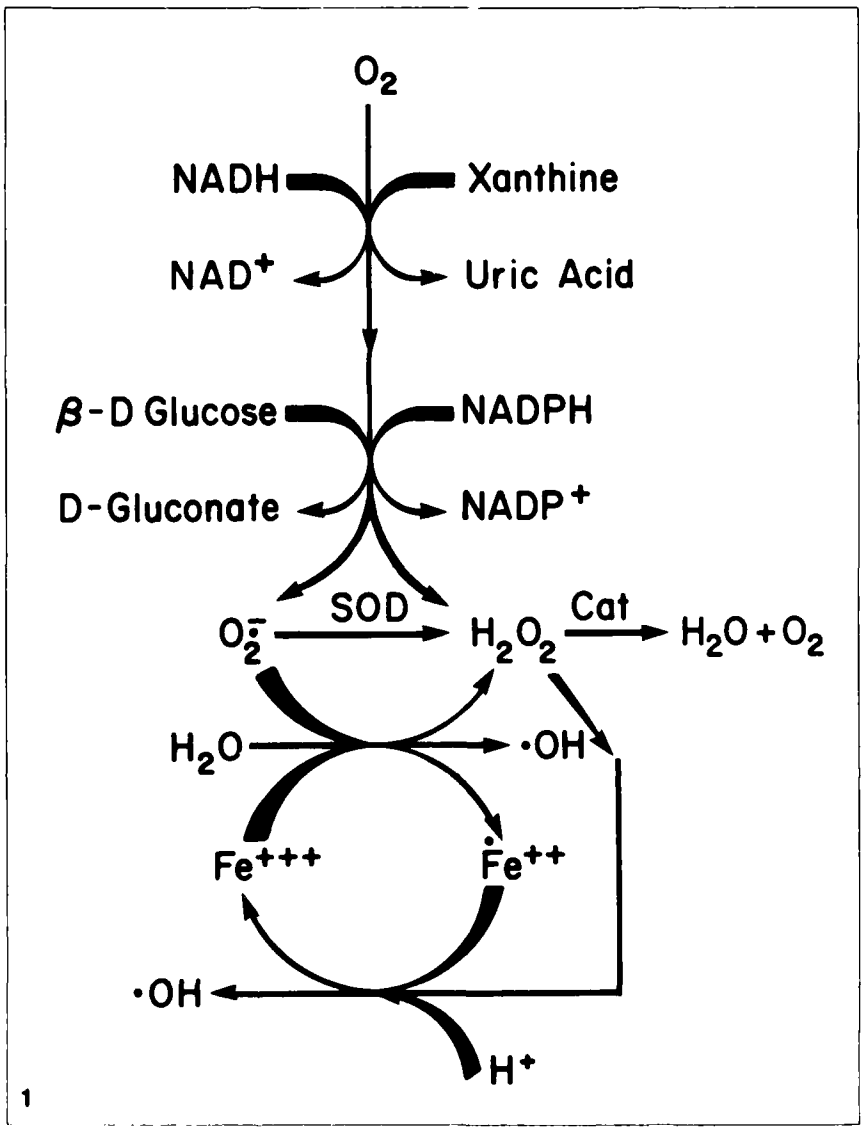


Fig. 1. *Hypothetical biochemical pathways for generation of hydroxyl (HO·) radicals during reperfusion following cardiac arrest, illustrating the crucial role of iron (Fe). Elimination of superoxide radicals by the action of superoxide dismutase (SOD) and catalase (cat) normally predominates. When O_2^- radicals are produced in abundance during reperfusion, some are shunted via the iron-dependent pathway (Haber-Weiss reaction), generating more of the chemically damaging hydroxyl radicals. The dot associated with the Fe++ symbol emphasizes its radical-like nature.*

positive pressure ventilation. Ventilation was discontinued at the initiation of cardiac arrest. CPR was begun after seven minutes, and animals having return of spontaneous circulation were entered into the study. Drug treatment was given to animals in the experimental group, and included was the iron chelator deferoxamine (50 mg/kg IV), injected within five minutes after cardiac resuscitation.

The results showed a 100% increase in survival of deferoxamine-treated rats compared to control rats ($P < .005$). After 15 days, there was no detectable neurologic deficit among survivors in either the control or the treated group. Deferoxamine thus doubled the probability of long-term, neurologically intact survival. Since the development of modern CPR methods in the 1960s, the only interventions shown to produce comparable improvement in long-term survival in any animal model or in man have been the use of adrenergic drugs, such as epinephrine,[13,14] and the use of early electrical defibrillation in cases of ventricular fibrillation.[15,16]

Because deferoxamine is administered after return of spontaneous circulation, the results are consistent with the hypothesis that a substantial amount of preventable tissue damage leading to death is occurring in control animals during the reperfusion phase. These encouraging results led us to formulate a detailed biochemical hypothesis to describe potential iron-mediated lipid peroxidation and related reactions in vivo during tissue ischemia and subsequent reperfusion. Presented is the specific mechanisms of this working hypothesis of iron-mediated tissue injury during reperfusion, and review evidence from the literature in support of the hypothesis.

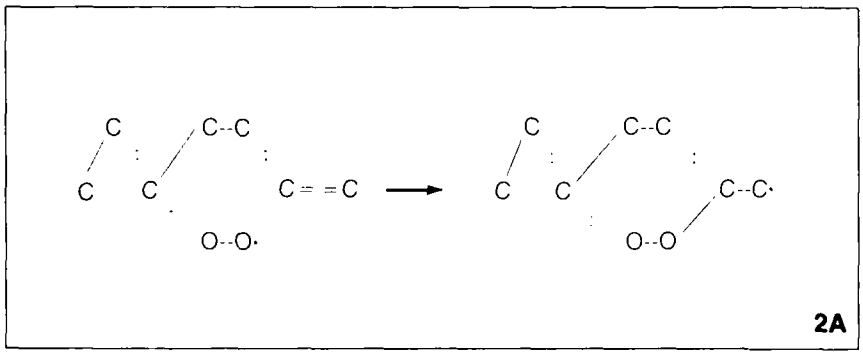
TABLE. *Ten day survival in rats following experimental cardiorespiratory arrest and CPR*

Response	Controls	Treated
Alive	14 (31%)	28 (62%)
Dead	31 (69%)	17 (38%)

[illegible] $P < .005$

Biochemical Hypothesis

The general features of our working hypothesis are as follows: 1) superoxide radicals (O_2^-) are produced in excess during the reperfusion phase, due to the abundance of reducing equivalents such as NADPH, the action of xanthine oxidase and NADPH-cytochrome P-450 reductase, the sudden reappearance of molecular oxygen, and other factors, 2) during the period immediately after reperfusion,



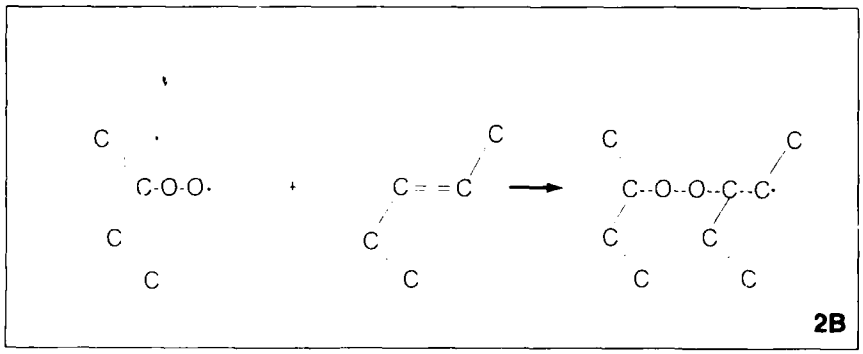


Fig. 2. *In the presence of double bonds in fatty acid chains, interesting cyclization reactions (eg, A) and cross-bridging reactions (eg, B) are possible.*

superoxide dismutase, together with catalase and other systems that normally destroy superoxide ions, are overwhelmed; the concentration of superoxide radicals rises sharply, and some are converted to highly deleterious hydroxyl radicals (HO·) by iron-catalyzed reactions; 3) hydroxyl radicals attack protein and lipid components of the cell, causing widespread chain reactions that alter molecular architecture; and 4) in some cases, these reactions may result in liberation of more free iron ions from ferritin molecules as well as damage to lysosomal membranes, leading to acceleration of the process.

We surmise that chelation of intracellular free iron by deferoxamine blocks steps 2 through 4 in this sequence, leading to reduced tissue damage during reperfusion. The specific steps of this proposed pathological chemistry are presented in order to show how iron-dependent chain reactions, involving common intracellular species, might lead to progressive cellular injury following initially successful resuscitation.

Initiation: Creation of Free Radical Species

Free radicals are molecules that contain an unpaired electron (represented here by the symbol ·). If a radical reacts with a nonradical molecule, then another free radical must be produced. This characteristic enables free radicals to participate in chain reactions that may be tens to thousands of events long.[1,18]

In postischemic tissues, in which reducing equivalents have accumulated during ischemia and in which oxygen becomes abundant during reperfusion, superoxide radicals may form as follows, in the presence of reduced flavoprotein, catalyzed by the enzyme NADPH-cytochrome P-450 reductase:[18,19]

$$2\ O_2 + NADPH \rightarrow NADP^+ + H^+ + 2\ O_2^-$$

Another source of O_2^- radicals in postischemic tissue is the action of xanthine oxidase on xanthine, which accumulates during ischemia. The sudden flush of oxygen during reperfusion, especially if O_2 therapy is given, drives these reactions to generate a burst of O_2^- radicals that exceeds the capacity of physiological defense systems, such as superoxide dismutase, to remove them.

Once O_2^- radicals appear in excessive concentration, the generation of the very reactive hydroxyl radical HO· may occur by the superoxide-driven, iron-catalyzed Haber-Weiss reaction:[7,18,20]

$$O_2^- + Fe^{+++} \rightarrow O_2 + Fe^{++}$$
$$2\ O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$
$$H^+ + Fe^{++} + H_2O_2 \rightarrow HO^\cdot + Fe^{+++} + H_2O$$

Ferritin, cytochromes in mitochondria, and other iron-containing enzymes provide intracellular stores of iron that may liberate sufficient free ionic iron for catalysis. Moreover, in newly reperfused tissues, there is a relative abundance of H+ ions, due to lactic acidosis and hypercarbia (Figure 1). The Haber-Weiss reaction is particularly interesting, given the protective effect that we found following ischemia and reperfusion of the iron chelator deferoxamine.

Propagation

The next step in the proposed pathogenic mechanism for reperfusion injury is the attack on intracellular proteins and lipids by the HO· radicals. The highly reactive hydroxyl radicals can attack membranes of diverse organelles. Reactions with water itself do not consume HO· because the HO· species is regenerated:

$$HO^\cdot + HOH \rightarrow HOH + {}^\cdot OH$$

Hydroxyl radicals can modify proteins and other organic molecules in several ways. For example, the encounter of HO· radicals with the hydrophobic portions of membrane lipids (especially at sites of double bonds)[21] may generate lipid radicals:

$$HO^\cdot + LH \rightarrow HOH + L^\cdot$$

Once formed, these lipid radicals can propagate through the membrane in what one might imagine is a wavelike fashion, from tail to tail of adjacent lipid molecules in the membrane:

$$L^\cdot + LH \rightarrow LH + L^\cdot$$

Then, in the presence of oxygen,

$$L^\cdot + O_2 \rightarrow LOO^\cdot \text{ and}$$
$$LOO^\cdot + LH \rightarrow LOOH + L^\cdot$$

a self-propagating sequence for lipid

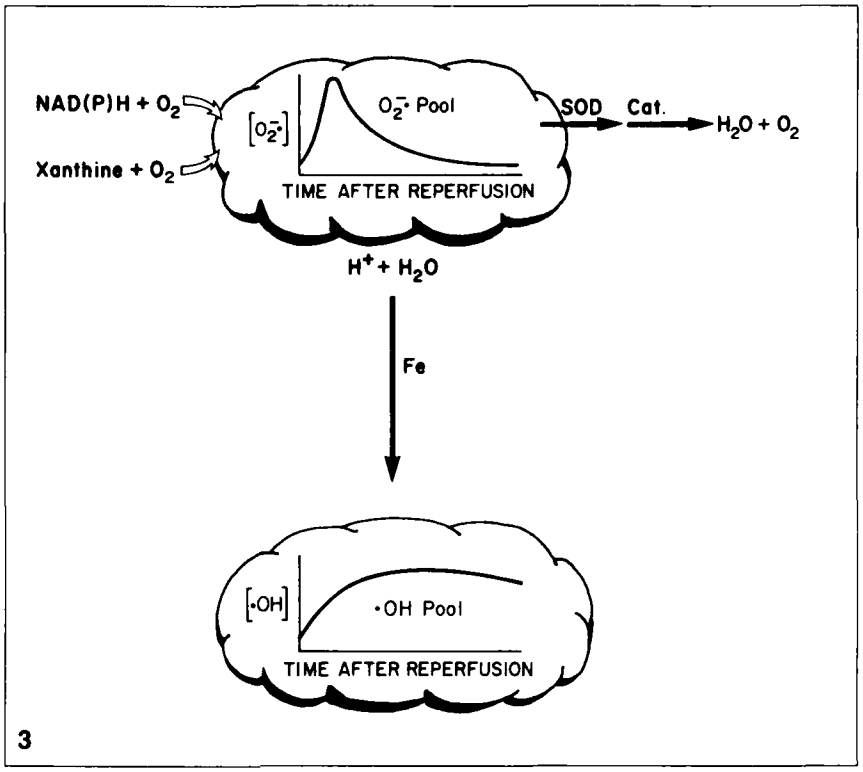


Fig. 3. *A conceptual model for the role of iron in the pathogenesis of postresuscitation tissue injury. Increased concentration of oxygen at beginning of reperfusion reacts with accumulated NADH, NADPH, and xanthine to produce an abnormal peak in the population of superoxide ions, which temporarily overwhelms normal pathway (via SOD and catalase) for their removal. Superoxide ions are converted to hydroxyl radicals via iron-dependent pathways. Normal mechanisms that scavenge free radicals are overwhelmed by the sudden burst of HO· radicals. The hydroxyl radicals modify numerous biological compounds via radical chain reactions.*

peroxidation.

Many other variations of this theme are possible; for example, carboxylation of membrane lipids may occur:

$$HO\cdot + LH \rightarrow HOH + L\cdot$$
$$L\cdot + CO_2 \rightarrow LCOO\cdot$$
$$LCOO\cdot + HOH \rightarrow LCOOH + HO\cdot$$

or

$$L\cdot + CO_2 \rightarrow LCOO\cdot$$
$$LCOO\cdot + LH \rightarrow LCOOH + L\cdot$$

This reaction might be especially important in reperfusion injury, because CO_2 is highly soluble in membrane lipids. CO_2 is relatively abundant in vivo, especially in hypoperfused tissues. Either carboxylation or peroxidation would place a hydrophilic group on interior alkyl chains of membrane fatty acids, causing them to reorient toward the aqueous phase, rending a defect in the membrane. This lipid carboxylation may be detectable experimentally by radiolabeled $^{14}CO_2$ incorporation into fatty acids.

In the presence of double bonds in fatty acid chains, interesting cyclization reactions are possible[18] (Figure 2A), as are cross-bridging reactions (Figure 2B).

By similar mechanisms, membrane-bound enzymes also can be attacked. All of these reactions are likely to be damaging to cell membrane structure and function and, to the extent that they are common, will lead to progressive membrane dysfunction, loss of selective permeability, and degradation of membrane-bound enzyme activity. Such reactions that are highly destructive to membranes may be especially significant in the lipid-rich white matter of the brain. Because secondary radical species are formed as radical chain reactions propagate, initiating species do not have to exist in high concentrations to do substantial damage over time.

Termination

Various termination reactions lead to stable, nonradical products. These include:

$$L\cdot + L\cdot \rightarrow L\text{-}L$$
$$LOO\cdot + L\cdot \rightarrow L\text{-}O\text{-}O\text{-}L$$
$$L\cdot + HO\cdot \rightarrow LOH$$

Reactions that involve collision of two radicals are much less likely to occur than propagation reactions involving radical and abundant, nonradical species. In biological membranes, termination reactions also include reaction between lipid radicals and membrane constituents, such as alpha-tocopherol, cholesterol, and sulfhydryl groups of glutathione and proteins.[18]

A summary of this theoretical model for the role of iron in the pathogenesis of postresuscitation tissue injury is shown (Figure 3). A temporary imbalance in the kinetics of superoxide ion formation versus degradation during reperfusion begins the sequence of pathological chemistry. The sudden rise in production of superoxide ions overwhelms the available superoxide dismutase and other defense systems, permitting the conversion of superoxide to more chemically destructive hydroxyl radicals. In the presence of free intracellular iron, HO· radicals form at a much faster rate than without iron. Thus a pool of HO· radicals is formed that produces a smoldering degradation of diverse cellular macromolecules. The deleterious process can accelerate in some tissues, for radical injury to lysosomes releases hydrolytic enzymes and radical injury to ferritin molecules releases more free iron.

Generation of $O_2^{\cdot-}$ Ions

Superoxide can be formed in a number of oxidation-reduction reactions in cells. Almost all aerobic organisms that have been studied have one or more superoxide dismutases,[22] which appear to have evolved to protect the organism from the toxic effects of oxygen and superoxide. Superoxide and hydrogen peroxide are formed continuously by the electron

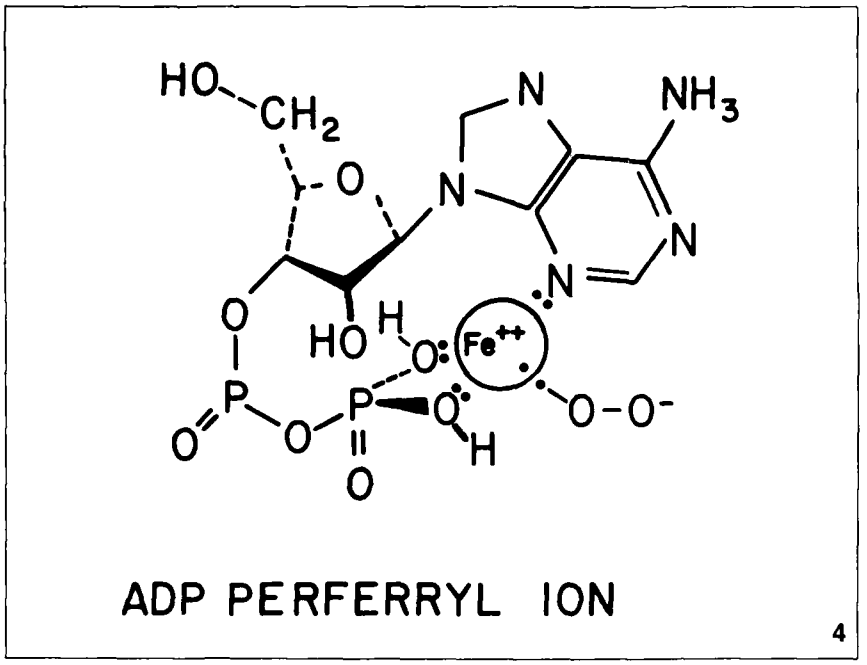


Fig. 4. *The ADP perferryl radical.*

transport chain,[23] but mitochondria seem to be protected against normal levels of these endogenously generated chemical species.

Several oxidative enzymes, including xanthine oxidase, are known to produce superoxide radical as a normal product.[24,25] Xanthine oxidase, which generates O_2^- and H_2O_2 during its conversion of xanthine to urate, often is used for in vitro peroxidation studies as a convenient O_2^- source.[24] There is evidence that xanthine dehydrogenase is converted in vivo to xanthine oxidase during ischemia, so that at the onset of reperfusion, when oxygen is reintroduced into the tissue, xanthine oxidase activity is especially high.[1]

Hypoxanthine, as well as xanthine, can serve as an oxidizable purine substrate for xanthine oxidase.[1] Interestingly hypoxanthine concentrations in the cat brain increase substantially during prolonged ischemia.[26] The action of an augmented xanthine oxidase pool on such an increased amount of hypoxanthine during reperfusion may give rise to enhanced production of superoxide radicals. Moreover, because the overall equation for oxidative phosphorylation is

$$NADH + H^+ + 3ADP + 3P_i + \tfrac{1}{2}O_2 \rightarrow NAD^+ + 4H_2O + 3ATP^{27}$$

reducing equivalents NADPH and NADH also accumulate during anoxia. Another major source of superoxide in postischemic tissues may be partial reduction of oxygen by these reducing equivalents.

Availability of Free Intracellular Iron

Iron is an important, normal constituent of the intracellular environment. It is an essential cofactor of many enzymes, including microsomal cytochrome P450, dioxygenases, pteridine-linked mono-oxygenases, xanthine dehydrogenase, superoxide dismutases, catalase, and peroxidase.[28] The major stores of intracellular iron are found within the protein ferritin, a hollow, spheroidal shell (molecular weight, 440,000) capable of holding 0 to 4,500 Fe atoms per molecule. Ferritin has six "windows" for exchange of Fe ions,[28] and is present in virtually all mammalian cells.

Sirivech et al (1974) have shown that the most rapid release of iron from ferritin is observed under anaerobic conditions.[29] This free iron may accumulate during ischemia, setting the stage for reperfusion injury. The very recent work of Nayini et al has demonstrated a three-fold increase in non-protein-bound "low molecular weight chelate iron" to 0.4 μM/g in brain tissue of dogs two hours after resuscitation from 15 minutes of cardiac arrest, compared to nonischemic controls.[30] Moreover, studies in vitro just completed by Thomas and coworkers suggest that superoxide can directly mediate the reductive release of iron from ferritin.[31]

Crucial Role of Iron

Although there are many possible initiation mechanisms for free-radical-mediated lipid peroxidation, virtually all that have been proposed involve iron. There is general agreement that tissue homogenates from brain, liver, and kidney readily undergo peroxidation, and that iron, oxygen, and a reducing agent such as NADPH are essential ingredients for initiation of lipid peroxidation in vitro.[18,20,25,32] The chemical mechanism most commonly proposed for initiation of lipid peroxidation involves iron-catalyzed, Harber-Weiss chemistry.[4,18,24,25]

Phosphates, which are abundant intracellularly, are important expeditors of initiation reactions, as shown by Tien and Aust,[33] who found a four-fold increase in in vitro lipid peroxidation catalyzed by either microsomes or xanthine oxidase with the addition of ADP. Moreover, the pH optimum for iron-phosphate-dependent lipid peroxidation in vitro ranges from 7.0[34] to 7.5,[35] a pH range likely to occur in postischemic tissues. On the other hand, deferoxamine inhibits iron-catalyzed formation of hydroxyl radicals from superoxide, and the ferrioxamine complex (ie, iron-deferoxamine) is chemically inert in in vitro lipid peroxidation.[19,36]

The only real controversy in the biochemical literature on this subject concerns whether hydroxyl radicals are absolutely necessary intermediaries in the initiation of lipid peroxidation. Aust et al[33] and Sugioka et al[37] have studied two in vitro systems that did not contain phosphate buffer in which they were unable to demonstrate evidence for participation of HO· radicals in lipid peroxidation. Under these circumstances, they have proposed that initiation of lipid peroxidation is mediated by the "ADP-perferryl ion," which abstracts hydrogen directly from polyunsaturated fatty acids without the intermediate participation of water or HO· (Figure 4).

Sugioka and coworkers did find evidence of HO· generation when the in vitro reaction was run in phosphate

buffer, and the amount of $HO^{\cdot}$ detected was proportional to the amount of phosphate over the range of 0 to 150 mM.[37] Because of the high concentration of intracellular phosphates (about 50 mM), Haber-Weiss chemistry seems more likely in vivo. The Fenton and ADP-perferryl ion mechanisms are not mutually exclusive and may, in fact, operate together. Both depend on iron.

Structural Damage by Radical Chain Reactions

There is considerable evidence that ischemic membrane injury in liver and myocardium is associated with degradation of membrane phospholipids,[4] including those of the lysosomal and mitochondrial membranes. Such damage would result in accelerated deterioration of the cell. The radical mechanisms described are fully capable of producing such membrane damage, as indicated by the classic example of radiation-induced necrosis. The primary products of the radiolysis of water are the free radicals $H^{\cdot}$ and $HO^{\cdot}$, which are widely believed to play an important pathogenic role. Carbon-tetrachloride-induced liver cell necrosis is also commonly believed to be the result of free radical injury, initiated by the action of cytochrome P450 on CCl_4.[4]

Hillered and Ernster[34] have shown that brain mitochondria exposed to oxygen radicals in vitro show an inhibition of respiratory activity similar to that reported by other investigators following transient cerebral ischemia in vivo. Artman and coworkers,[40] studying an isolated heart model of acute ferrous sulfate poisoning, have shown that the 50% depression of function produced after 90 minutes of exposure to 1.8 mM iron is a consequence of free radical generation. Evidence for the role of superoxide and hydroxyl radicals has been reported recently for postischemic reperfusion injury of the cat small intestine[38] and dog myocardium.[39,40] Thus there is reason to believe that free radical reaction chains can produce substantial and significant damage to cell structure and function, damage sufficient to explain the death of the control rats in our preliminary study.

Conclusion

The value of any hypothesis lies in its ability to explain known phenomena and to provide a basis for further experiments. The biochemical hypothesis presented here accounts for damage occurring after reperfusion rather than during ischemia, and it explains why such damage does not necessarily occur at other times. It also explains why a single bolus dose of iron chelator at the beginning of reperfusion might be protective by blocking the iron-dependent reactions during the time of the transient peak in superoxide concentration. The nature of the reactions described is consistent with the gradual, progressive decline after initially successful resuscitation that was observed in our animal models and that has been pointed out by White.[2]

The hypothesis also suggests several interesting experiments, such as the detection of lipid carboxylation in postischemic brain by incorporation of radiolabeled carbon dioxide. Others include therapeutic trials in animal models with the xanthine oxidase inhibitor allopurinol to decrease formation of superoxide radicals by xanthine oxidase, and therapeutic trials in animal models with mannitol, a hydroxyl radical trapping agent. Both of these drugs are clinically available and safe, and may offer a fresh approach for improved results in cardiopulmonary cerebral resuscitation. Most important, the hypothesis lends credibility to further preclinical research with deferoxamine and other iron chelators, which promise to block the critical step in the initiation of reperfusion injury.

The author acknowledges the helpful comments and suggestions made by Bernard Axelrod, Steven Aust, and Blaine White.

References

1. McCord JM: Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985;312:159-163.

2. White BC, Aust SD, Artors KE, et al: Brain injury by ischemic anoxia: Hypothesis extension — a tale of two ions? *Ann Emerg Med* 1984;13:862-867.

3. Ames A, Wright L, Kowada M, et al: Cerebral ischemia, II. The no-reflow phenomenon. *Am J Pathol* 1968;52:437-438.

4. Farber JL: Minireview: The role of calcium in cell death. *Life Sci* 1981;29:1289-1295.

5. White BC, Winegar CD, Wilson RE, et al: Possible role of calcium blockers in cerebral resuscitation: A review of the literature and synthesis for future studies. *Crit Care Med* 1983;11:202-207.

6. Babbs CF: Improved methods of resuscitation from sudden cardiac death: research opportunities for emergency physicians. *Emergency Medicine Survey* 1982;103-108.

7. Bulkley GB: The role of oxygen free radicals in human disease processes. *Surgery* 1983;94:407-411.

8. McCord JM: The superoxide free radical, its biochemistry and pathophysiology. *Surgery* 1983;94:412-414.

9. Myerburg RJ, Conde CA, Mayorga-Cortes A, et al: Clinical, electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. *Am J Cardiol* 1980;68:568-576.

10. Liberthson R, Nagel E, Hirschmann J: Prehospital ventricular defibrillation: Prognosis and followup course. *N Engl J Med* 1974;291:315.

11. Badylak SF, Babbs CF: Effects of carbon dioxide, lidoflazine, and deferoxamine administered after cardiorespiratory arrest and CPR in rats, abstract. *Ann Emerg Med* 1985;14:509.

12. Kompala SD, Babbs CF: Effect of deferoxamine on late deaths following cardiopulmonary resuscitation in rats, abstract. *Ann Emerg Med* 1985;14:509.

13. Pearson JW, Redding JS: The role of epinephrine in cardiac resuscitation. *Anesth Analg* 1963;42:599-606.

14. Otto CW, Yakaitis RW, Redding JS, et al: Comparison of dopamine, dobutamine, and epinephrine in CPR. *Crit Care Med* 1981;9:366.

15. Eisenberg MS, Bergner L, Hallstrom A: Cardiac resuscitation in the community. *JAMA* 1979;241:1905-1907.

16. Eisenberg MS, Bergner L, Hallstrom A: Out-of-hospital cardiac arrest: Improved survival with paramedic services. *Lancet* 1980;2:812-815.

17. Eisenberg MS, Nagel EL, Hearne T, et al: Sudden cardiac arrest in the community, in Jacobson S (ed): *Resuscitation*. New York, Churchill Livingstone, 1983, pp 13-26.

18. Aust SD, Svingen BA: The role of iron in enzymatic lipid peroxidation, in *Free Radicals in Biology, Vol V*. New York, Academic Press, 1982, pp 1-28.

19. Morehouse LA, Thomas CE, Aust SD: Superoxide generation by NADPH-cytochrome P-450 reductase: The effect of iron chelators and the role of superoxide in microsomal lipid peroxidation. *Arch Biochem Biophys* 1984;232:366-377.

20. Tien M, Svingen BA, Aust SD: An investigation into the role of hydroxyl radical in xanthine oxidase-dependent lipid

peroxidation. *Arch Biochem Biophys* 1982;216:142-151.

21. Tien M, Aust SD: Rabbit liver microsomal lipid peroxidation: The effect of lipid on the rate of peroxidation. *Biochim Biophys Acta* 1982;172:1-9.

22. Fridovich I: Superoxide radical: An endogenous toxicant. *Ann Rev Pharmacol Toxicol* 1983;23:239-257.

23. Fridovich I, Boveris A: Mitochondrial production of superoxide radical and hydrogen peroxide. *Adv Exp Med Biol* 1977;78:67-82.

24. Hillered L, Ernster L: Respiratory activity of isolated rat brain mitochondria following in vitro exposure to oxygen radicals. *J Cereb Blood Flow Metab* 1983; 3:207-214.

25. Mead JF: Free radical mechanisms of lipid damage and consequences for cellular membranes, in Prior WA (ed): *Free Radicals in Biology, Vol I.* New York, Academic Press, 1976, pp 51-68.

26. Kleihues P, Kobayashi K, Hossmann KA: Purine nucleotide metabolism in the cat brain after one hour of complete ischemia. *J Neurochem* 1974;23:417-425.

27. Lehninger AL: *Biochemistry*, ed 2. New York, Worth Publishers, Inc, 1975, p 515.

28. Crichton RR: Interactions between iron metabolism and oxygen activation. *Excerpta Medica* 1979;57-76.

29. Sirivech S, Frieden E, Osaki S: The release of iron from horse spleen by reduced flavins. *Biochem J* 1974;143:311-315.

30. Nayini NR, White BC, Aust SD, et al: Post resuscitation iron delocalization and malondialdehyde production in the brain following cardiac arrest. *Free Radicals Biol Med*, 1985, in press.

31. Thomas CE, Morehouse LA, Aust SD: Ferritin and superoxide-dependent lipid peroxidation. *J Biol Chem*, 1985, in press.

32. Tien M, Aust SD: Comparative aspects of several model lipid peroxidation systems. *Lipid Peroxides in Biology and Medicine* 1982;23-39.

33. Tien M, Svingen BA, Aust SD: Initiation of lipid peroxidation by perferryl complexes, *Oxygen and Oxy-radicals in Chemistry and Biology*. New York, Academic Press, 1981, pp 147-152.

34. Bucher JR, Tien M, Morehouse LA, et al: Three mechanisms for the formation of an initiator of lipid peroxidation by xanthine oxidase. *Oxy Radicals and Their Scavenger Systems* 1983;1:296-299.

35. Bucher JR, Tien M, Morehouse LA, et al: Influence of superoxide dismutase and catalase on strong oxidant formation during autoxidation of ferrous chelates. *Oxy Radicals and Their Scavenger Systems* 1983;1:292-295.

36. Gutteridge JMC, Richmond R, Halliwell B: Inhibition of the iron-catalyzed formation of hydroxyl radicals from superoxide and lipid peroxidation by desferrioxamine. *Biochem J* 1979;184:469-472.

37. Sugioka K, Nakano H, Nakano M, et al: Less involvement of hydroxyl radical and a great importance of proposed perferryl ion complexes in lipid peroxidation. *Biochim Biophys Acta* 1983;753:411-421.

38. Parks DA, Bulkley GB, Granger DN, et al: Ischemic injury in the cat small intestine, role of superoxide radicals. *Gastroenterology* 1982;82:9-15.

39. Gardner TJ, Stewart JR, Casale AS, et al: Reduction of myocardial ischemic injury with oxygen derived free radicals. *Surgery* 1983;94:423-427.

40. Artman M, Olson RD, Boucek RJ, et al: Depression of contractility in isolated rabbit myocardium following exposure to iron: Role of free radicals. *Toxicol Appl Pharmacol* 1984;72:324-332.

ADVERTISERS' INDEX

MAST®

(MEDICAL ANTI-SHOCK TROUSERS)

CONTROL SHOCK.. SAVE LIVES

The MAST* (Medical Anti-Shock Trousers) can:

- Control or Reverse Shock
- Provide Rapid Autotransfusion
- Check Trauma

MAST* (developed by the David Clark Company, Inc.) is the first, the original Medical Anti-Shock Trouser:

- Fast...Applied in 60 Seconds

MAST* is used in:

- Accidents, Trauma, Surgery, In Patient and ICU
- Emergency Rooms

Also available: the Tod-mast will fit a toddler within the ages of two to four years, and Pedi-mast will fit children in a size range between 46"-58" in height.

mast® III-A

FEATURES:
- Automatic Relief Valves
- Removable Air Chambers
- Field Maintainable

mast® III-AT
TRANSPARENT

FEATURES: Same as MAST* III-A and AM
PLUS:
- Facilitates Examination Allows You To...
- Observe the Injury
- Monitor Skin Condition
- Easy Access to Femoral Artery

mast® III-AM
MODULAR

FEATURES: Same as MAST* III-A
PLUS:
- Easy Access to Femoral Artery

Patent No. 3933150
National Stock No. 6515-01-076-4713

MAST is the Registered Trademark of the*

David **Clark** COMPANY
INCORPORATED

360 Franklin Street, Worcester, MA 01604
(617) 756-6216 *Telex 920482*

cause of emergency pain...

Myocardial Infarction

NUBAIN® IM IV SC

nalbuphine HCl

Safe, potent analgesia.

NUBAIN provides all the analgesic efficacy of morphine, plus:

[ ] Documented ceiling effect in dose-related respiratory depression[1]
[ ] Superior hemodynamic profile[2]
[ ] Lower incidence of nausea, vomiting, and psychotomimetic effects[3]
[ ] Non-scheduled

And NUBAIN provides up to six hours of pain relief with every dose, reducing the need for repeated injections. So whatever the cause of emergency pain, it makes sense to rely on NUBAIN. Now available in 20 mg/ml ampul, vial, and syringe as well as 10 mg/ml ampul and vial.

For further information concerning contraindications, side effects, and precautions, please see following page.

NUBAIN is available exclusively from Du Pont.

Du Pont Pharmaceuticals, Inc.

DUPONT

How well are you communicating with your PATIENTS?

Patient compliance—how well patients follow instructions about taking prescription drugs—is something that worries health professionals, according to a recent Harris survey. And with good reason. A number of studies have shown that a third to a half of all drugs are taken improperly. Yet a Chilton survey found that only 2 to 4 percent of patients question their doctors about drugs prescribed for them.

It's up to health-care providers to open up the dialogue about prescription drugs. When you write, dispense or check on a prescription, make sure your patient knows:

- **The name** of the drug
- **Its purpose**—what conditions does it treat?
- **How and when** to take the drug—and when to stop taking it
- What **food, drinks and other drugs to avoid** while taking it
- What **side effects** may result—are they serious, short-term, long-term, etc.?

■ *A message from the Food and Drug Administration.*

Whatever the cause of emergency pain...

NUBAIN™ IM IV SC
nalbuphine HCl

Brief Summary of Prescribing Information

INDICATIONS For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia as a supplement to surgical anesthesia and for obstetrical analgesia during labor.

CONTRAINDICATIONS NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated. Care should be taken to avoid inadvertent excessive dosage or frequent administration which in susceptible individuals might result in physical dependence. Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal (i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and pilomotion). **Use in Ambulatory Patients** NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks (such as driving a car or operating machinery). Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards. **Use in Emergency Procedures** Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks. **Use in Children** Clinical experience to support administration to patients under 18 years of age is not available at present. **Use in Pregnancy (other than labor)** Safe use of NUBAIN in pregnancy has not been established. Animal reproduction studies have not revealed teratogenic or embryocidal effects. Nalbuphine should be administered to pregnant women only if the judgement of the physician, the potential benefit outweighs the possible hazard. **Use During Labor and Delivery** NUBAIN, as with other narcotic analgesics, may cause respiratory depression of the neonate. It should be used with caution in women delivering premature infants. **Head Injury and Increased Intracranial Pressure** The [illegible] potential of patient [illegible] resulting from vasodilation following administration [illegible] perceptual changes often exhibited by patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution. **Interaction With Other Central Nervous System Depressants** Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before or concurrently or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiratory function from other medications, trauma, head injury, severe asthma, severe chronic obstructive respiratory disease. **Impaired Renal or Hepatic Function** Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may require [illegible]. Therefore, in the presence of such conditions, NUBAIN should be used with caution and a reduced dose. **Myocardial Infarction** As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have [illegible] ventricular dysfunction. **Biliary Tract Surgery** As with other [illegible] NUBAIN should be used with caution in patients undergoing biliary tract surgery. [illegible] spasm of the sphincter of Oddi.

ADVERSE REACTIONS The most frequently [illegible] associated with NUBAIN [illegible] are usually transient and rarely require discontinuation of therapy. [illegible] **CNS Effects** [illegible] **Cardiovascular** [illegible] **Gastrointestinal** Cramps, dyspepsia, bitter taste. **Respiration** Depression, dyspnea, asthma. **Dermatological** Itching, burning, coldness. **Miscellaneous** Speech difficulty, urinary urgency, blurred vision, flushing and warmth. **Patients Dependent on Narcotics** Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN® (nalbuphine HCl). If unduly troublesome narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine until relief occurs. If the previous analgesic was morphine, meperidine, codeine or other narcotic with similar duration of activity, one fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal (i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or pilomotion). If untoward symptoms do not occur, progressively larger doses may be used at appropriate intervals until the desired level of analgesia is obtained with NUBAIN. **Management of Overdosage** The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated. The administration of single doses of 10 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

NARCAN® is a registered U.S. trademark of Du Pont Pharmaceuticals, Inc. [illegible]

References 1. [illegible] 2. [illegible] 3. [illegible]

Du Pont Pharmaceuticals, Inc.
[illegible]

DUPONT

SPECIAL CONTRIBUTION

brain ischemia, brain resuscitation, calcium antagonists, cardiopulmonary resuscitation, thiopental

Ischemic Brain Protection

Nicholas G Bircher, LT, MC, USNR
Bethesda, Maryland

From the Anesthesia Department, Naval Hospital, and Department of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, and the Resuscitation Research Center and Department of Anesthesiology Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985

The opinions expressed herein are those of the author, and are not to be construed as reflecting the views of the Navy Department, or the Naval Service at large, or of the Department of Defense.

Address for reprints: Nicholas G Bircher, LT, MC, USNR, Anesthesia Department (61), Naval Hospital, Naval Medical Command, National Capital Region, Bethesda, Maryland 20814-5011

Despite advances in the understanding of the pathophysiology of cerebral ischemia, no single brain resuscitation therapy has yet been shown to be clinically superior to brain-oriented intensive care. Basic concepts in cardiopulmonary-cerebral resuscitation (CPCR) are discussed, as are two specific phases of CPCR, cerebral preservation and cerebral resuscitation. Cerebral preservation is initiated during cardiac arrest (ie, prior to restoration of spontaneous circulation [ROSC]) and includes use of artificial perfusion techniques and drugs to produce cerebral perfusion during this phase. Cerebral resuscitation is brain-oriented therapy initiated after ROSC. Pharmacologic agents currently under study for cerebral resuscitation include the barbiturates, calcium antagonists, and iron chelators. With respect to defining efficacy of the pharmacologic agents, the concept of therapeutic window is important. Although no agent has been proven clinically, several appear to be promising. [Bircher NG: Ischemic brain protection. Ann Emerg Med August 1985;14:784-788.]

Introduction

It is important to review and update a few basic concepts of brain resuscitation. The first of these is timing of therapy. In the broad sense, protection of the brain allows for a successful resuscitation — ie, the patient goes home neurologically intact. However, cerebral protection can be strictly defined as therapy that is instituted prior to a hypoxic or ischemic insult. It is important to avoid cerebral ischemia by aggressive monitoring and intervention, and there are several anesthetic agents and techniques that can protect the heart and brain if a period of ischemia or total circulatory arrest is anticipated.[1-3]

The emergency physician, however, seldom has the opportunity to protect the brain prior to cardiac arrest. Hence we focus on the two subsequent phases of cardiopulmonary-cerebral resuscitation (CPCR): cerebral preservation therapy instituted during cardiac arrest while attempting restoration of spontaneous circulation (ROSC), or while trying to correct cerebral ischemia or hypoxia of other etiologies; and cerebral resuscitation therapy instituted after ROSC.

Mechanisms of Cerebral Ischemic Injury

The mechanisms and degree of cerebral injury depend on the insult and its duration. Insults may be classified as ischemic, anoxic, hypoglycemic, metabolic, anemic, traumatic, hemorrhagic, inflammatory, or cancerous.[4] It is important to both the investigator and the practitioner that comparisons of therapy between studies be made only when the insults are similar. Each type of insult has a characteristic biochemistry and natural history, either or both of which may dictate appropriate therapy.[5-9] Ischemic insults may be complete (eg, cardiac arrest) or incomplete (shock, cardiac arrest with CPR). Mechanisms of injury may be classified into two broad categories, microvascular damage and derangement of cellular function. Microvascular damage results in the "no-reflow" phenomenon and cerebral hypoperfusion postischemia. Hypoxic damage to endothelial cells initiates platelet aggregation and thrombus formation; releases histamine, serotonin, prostaglandins, kinins, and complement components; and allows interstitial edema. All of these further impair oxygen delivery to the cell.[10] Autoregulation function in

cerebral vessels also is impaired. After a transient hyperemia, cerebrovascular resistance rises rapidly and further impairs perfusion.[11]

At the cellular level, complete ischemia causes exhaustion of oxygen stores within 30 seconds, and of glucose and ATP stores within five minutes of onset.[6] Ion pumps and cellular metabolism then fail. Severe cellular damage is heralded by the efflux of potassium and the influx of calcium. Pathologists have long recognized the significance of cytosolic calcium accumulation,[12] which appears to be mediated by failure of intracellular and membrane calcium homeostasis, as well as increased overall membrane permeability to calcium, independent of calcium slow channels. Failure of intracellular regulation of iron and superoxide ion (O_2^-) also exacerbate damage. All of the therapies discussed below are intended either to prevent the occurrence of these changes or to ameliorate their effects once they have occurred.

Among the problems with both experimental and clinical trials in this area is defining the therapeutic window. Some insults are too mild for differences in therapy to be detected; some are too severe to allow benefit. The therapeutic window is the range between these two extremes. Experimentally the investigator can map out the insults that are amenable to treatment. The practitioner sees a spectrum of patients and, currently, has no good way to know where a particular case falls on this continuum. The clinical investigator must try to exclude from clinical trials those patients who are outside the therapeutic window because these patients, by definition, cause the results of the study to gravitate toward the null hypothesis, that is, that the drug being tested has no effect. Careful construction of entry and exclusion criteria for clinical trials is essential.

Cerebral Preservation

Although experimental methods to improve artificial circulation during cardiac arrest recently have been investigated,[7,13,24] priority must still be given to restoration of spontaneous circulation. Patient outcome is improved by reducing insult time, which is the sum of arrest time (total circulatory arrest); cardiopulmonary resuscitation (CPR) time; and hypoxia time (the duration of tissue hypoxia prior to arrest and after ROSC). Maximum cerebral blood flow (CBF) achievable during CPR undergoes rapid, exponential decay as arrest time elapses prior to the initiation of CPR.[25,26] The first step in cerebral preservation is the rapid institution of standard CPR (SCPR), which seems to preserve the brain, at least briefly, if started soon after arrest.[27,28] The first step in cerebral resuscitation is to restart the heart.

Standard CPR is preferable to complete cardiac arrest, but cannot reliably preserve the heart and brain, as was once thought.[29,30] Typical CPR performance, moreover, often falls short of standard CPR as defined by the American Heart Association.[31,32] Although rate of compression and ratio of compressions to ventilation have little impact on blood flow, depth[33] and duration[34] of compression are major determinants of blood flow. The recommended duration of compression (50% of the compression/relaxation cycle)[29] and adequate depth of compression are important psychomotor skills that require greater emphasis in CPR training.

Recent research into the mechanism of blood flow during CPR has centered on the role of intrathoracic pressure.[35] Simultaneous ventilation-compression CPR (SVC-CPR) has been reported to increase CBF when compared to SCPR in dogs.[36,37] Our own studies show that when depth of compression during experimental SCPR is adjusted to produce optimal flow, superimposition of simultaneous ventilation and compression does not increase arterial pressure or flow, and can decrease cerebral oxygenation.[38] Because optimal peak intrathoracic pressure during chest compression has not been determined and is impossible to measure clinically, SVC-CPR must still be considered an experimental technique, although vest-binder CPR supplemented with correction of acidosis seems to offer good cerebral preservation over 30 minutes of CPR in dogs.[39]

Another approach to improving CBF is interposed abdominal compression CPR (IAC-CPR).[40] This technique offers promise, but the published increase in CBF from 11% to 13% of control may not be clinically significant.[41] A more promising approach for the patient in whom a prolonged resuscitation is appropriate is open-chest CPR (OCCPR). This technique maintains nearly normal CBF[42,43] and improves cerebral outcome in animals.[30]

Although experimental evidence strongly supports the superiority of OCCPR over SCPR,[44] it remains unclear which patients will benefit from OCCPR. We have suggested that any patient who fails to respond to conventional advanced cardiac life support (ACLS) in the first ten minutes of the resuscitation attempt may benefit from the additional cerebral and myocardial perfusion provided by OCCPR while attempts to restart the heart continue.[45] OCCPR and SCPR (both without epinephrine) have been compared and OCCPR improves cerebral outcome in dogs.[30] A study of SCPR with epinephrine should be done, however, because epinephrine is known to increase both cerebral and myocardial flow during SCPR and SVC-CPR.[46,47] This issue should be resolved in the laboratory and by randomized, prospective clinical trials, and OCCPR should be reevaluated for use during difficult resuscitations.

Cerebral Resuscitation

Although several agents and techniques have been suggested to offer benefit in the postischemic period, we will focus on only the barbiturates and the calcium antagonists. Considerable work has been done to suggest that iron chelation may be an important new area. Lately, tremendous effort has gone into brain resuscitation research, but demonstrable clinical benefit of any one agent remains elusive.

Bleyaert's initial report[48] of benefit from thiopental after global cerebral ischemia was both novel and provocative. Several investigators had previously shown barbiturates to be protective when given prior to ischemia,[3,49-54] and there was sufficient evidence to support a clinical trial to investigate the effects of thiopental after cardiac arrest in human beings. Several other investigators, using a variety of models, failed to demonstrate the benefit of barbiturates given after a period of cerebral ischemia.[55-58] This led to substantial controversy, and eventually to reinvestigation of the effects of thiopental in a primate model similar to Bleyaert's in the same laboratory.[59]

The key differences between Bleyaert's study and the subsequent

study by Gisvold were that Gisvold proceeded as follows: 1) he more closely controlled arterial pressure immediately postischemia; 2) he conducted control experiments concurrently; 3) he used mechanical ventilation for the same amount of time in both control and therapy groups; 4) he used lidocaine prophylactically in the thiopental group; and 5) he monitored blood glucose levels. Gisvold found no benefit to thiopental loading after 18 minutes of global cerebral ischemia.

The clinical question of whether thiopental was effective in brain resuscitation was addressed by the Brain Resuscitation Clinical Trial (BRCT I).[60] This was the first randomized, prospective, multi-institutional clinical trial of brain resuscitation, and it demonstrated that the administration of 30 mg/kg thiopental to patients not awakening within ten minutes of restarting the heart after cardiac arrest did not yield improved neurological outcome. Stratification after data collection, however, revealed that the patient subgroup with arrest times greater than five minutes was significantly improved. Further study may be indicated to clarify the therapeutic window of the barbiturates.

The drugs currently showing promise for brain resuscitation are the calcium antagonists. Verapamil is a familiar agent for supraventricular dysrhythmias; however, evidence is mixed concerning its value in brain resuscitation.[61-63] Flunarizine showed promise experimentally in terms of restoring cerebral blood flow after 20 minutes of cardiac arrest and reperfusion by cardiopulmonary bypass in dogs.[64] Untreated animals showed the characteristic no-reflow phenomenon. Investigation by Michenfelder using a model of total circulatory arrest failed to demonstrate any increase in CBF.[65] Moreover, neurological outcome was not improved compared to that of untreated dogs, and flunarizine produced pulmonary edema in five of six dogs studied. Another recent study of flunarizine reported improved neurological status after ten minutes of cardiac arrest in dogs, and no pulmonary edema.[66] Differences in postresuscitative care may be important in these studies. In addition, flunarizine has limited water solubility and the method and timing of its administration may be critical to avoid crystallization (BC White, personal communication, February 1985).

Nimodipine has been shown to be beneficial in a dog model of total circulatory arrest from temporary aortic ligation, and in a model of global brain ischemia in primates.[67] It doubled postischemic CBF, but had no effect on metabolism. The increase noted, from 25% to 45% of control (preischemic) CBF values, suggests that nimodipine improves outcome by raising the postischemic flow above the threshold of CBF needed to maintain neuronal viability. The threshold for the postischemic brain is not well known, but for the normal brain it is thought to be approximately 20% of normal CBF.[68]

Lidoflazine is another promising calcium antagonist. Winegar's report[69] of improved neurological outcome after 15 minutes of cardiac arrest in dogs was the first to document the effect of lidoflazine. Winegar anesthetized dogs with ketamine, which is not brain protective during ischemia,[70] caused cardiac arrest with potassium chloride, and then resuscitated the heart with internal cardiac compression, 10 mEq/kg of sodium bicarbonate, and an epinephrine drip. The reported benefit was unequivocal, but comparison to other studies is difficult.

Dean[71] found no change in CBF with lidoflazine after 12 minutes of cerebral ischemia induced by aortic cross-clamping, although the postischemic drop in CBF was not as dramatic as in some other models. Dean concluded that lidoflazine does not work by restoring CBF. Vaagenes[72] studied the effect of lidoflazine after ten minutes of ventricular fibrillation (VF), and found improvement in neurological outcome. He did not, however, demonstrate benefit after asphyxial arrest or after shorter periods of VF. Lidoflazine shows considerable promise and has fewer dangerous side effects than other calcium antagonists, but may have a narrow therapeutic window. The second phase of the Brain Resuscitation Clinical Trial (BRCT II) will examine possible benefits of lidoflazine administered to human beings remaining comatose ten minutes after restoration of spontaneous circulation following cardiac arrest. This trial is in progress and results will be available in 1986.

Conclusion

Our understanding of the postischemic brain has progressed substantially during the past ten years, yet no specific agent has been identified for clinical brain resuscitation. The best we have to offer is good general intensive care. One of the important lessons to emerge from the Brain Resuscitation Clinical Trials is that things go better when there is a plan: the presence of a protocol and a senior investigator seems to improve patient care. The search goes on for a brain resuscitation agent; there is light on the horizon.

References

1. Singler RC: Special techniques: Deliberate hypotension, hypothermia, and acute normovolemic hemodilution. In Gregory GA (ed): *Pediatric Anesthesia*. New York, Churchill Livingstone, 1983, pp 559-564.

2. Newberg LA, Michenfelder JD: Cerebral protection by isoflurane during hypoxemia or ischemia. *Anesthesiology* 1983;59:29-35.

3. Michenfelder JD, Theye RA: Cerebral protection by thiopental during hypoxia. *Anesthesiology* 1973;39:510-517.

4. Safar P: Resuscitation after brain ischemia, in Grenvik A, Safar P (eds): *Brain Failure and Resuscitation*. New York, Churchill Livingstone, 1981, pp 155-184.

5. Rehncrona S, Siesjo BK: Metabolic and physiological changes in acute brain failure, in Grenvik A, Safar P (eds): *Brain Failure and Resuscitation*. New York, Churchill Livingstone, 1981, pp 11-33.

6. Siesjo BK: Cell damage in the brain: A speculative synthesis. *J Cereb Blood Flow Metab* 1981;1:155-185.

7. Safar P: Recent advances in cardiopulmonary-cerebral resuscitation: A review. *Ann Emerg Med* 1984;13:856-862.

8. White BC, Aust SD, Artors KE, et al: Brain injury by ischemic anoxia: Hypothesis extension — A tale of two ions. *Ann Emerg Med* 1984;13:862-867.

9. Newberg LA: Cerebral resuscitation: Advances and controversies. *Ann Emerg Med* 1984;13:853-856.

10. McCuskey RS: Microcirculation: Basic considerations, in Cowley RA, Trump BF (eds): *Pathophysiology of Shock, Anoxia, and Ischemia*. Baltimore, Williams and Wilkins, 1982, pp 156-164.

11. Snyder JV, Nemoto EM, Carroll RG, et al: Global ischemia in dogs: Intracranial pressures, brain blood flow and metabolism. *Stroke* 1975;6:21-27.

12. Farber JL: Biology of disease: Membrane injury and calcium homeostasis in the pathogenesis of coagulative necrosis. *Lab Invest* 1982;47:114-123.

13. Redding JS: Abdominal compression

in cardiopulmonary resuscitation. *Anesth Analg* 1971;50:668-675.

14. Bircher N, Safar P, Stewart R: A comparison of standard, "MAST"-augmented, and open-chest CPR in dogs: A preliminary investigation. *Crit Care Med* 1980; 3:147-152.

15. Alifimoff JK, Safar P, Bircher N, et al: Cerebral recovery after prolonged closed-chest, MAST-augmented and open-chest cardiopulmonary resuscitation (CPR). *Anesthesiology* 1980;53(Suppl):S147.

16. Mahoney BD, Mirick MJ: Efficacy of pneumatic trousers in refractory prehospital cardiopulmonary arrest. *Ann Emerg Med* 1983;12:8-12.

17. Chandra N, Snyder LD, Weisfeldt ML: Abdominal binding during cardiopulmonary resuscitation in man. *JAMA* 1981; 246:351-353.

18. Chandra N, Rudikoff M, Weisfeldt ML: Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. *Lancet* 1980;1:175-178.

19. Chandra N, Weisfeldt ML, Tsitlik J, et al: Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high pressure simultaneous with chest compression. *Am J Cardiol* 1981; 48:1053-1063.

20. Sanders AB, Ewy GA, Alferness CA, et al: Failure of one method of simultaneous chest compression, ventilation and abdominal binding during CPR. *Crit Care Med* 1982;10:509-513.

21. Maier GW, Tyson GS, Olsen CO, et al: The physiology of external cardiac massage: High-impulse cardiopulmonary resuscitation. *Circulation* 1984;70:86-101.

22. Criley JM, Blaufuss AH, Kissel GL: Cough-induced cardiac compression: Self-administered form of cardiopulmonary resuscitation. *JAMA* 1976;236:1246-1250.

23. Bircher N, Safar P, Eshel G, et al: Cerebral and hemodynamic variables during cough-induced CPR in dogs. *Crit Care Med* 1982;10:104-107.

24. Sanders AB, Meislin HW, Ewy GA: The physiology of cardiopulmonary resuscitation: An update. *JAMA* 1984;252: 3283-3286.

25. Szmolenszky T, Szoke P, Halmagyi G, et al: Organ blood flow during external heart massage. *Acta Chir Acad Sci Hung* 1974;15:283-288.

26. Lee SK, Vaagenes P, Safar P, et al: Effect of cardiac arrest time on the cortical cerebral blood flow generated by subsequent standard external CPR in rabbits, abstract. *Ann Emerg Med* 1984;13:385.

27. Ritter G, Goldstein S, Leighton R, et al: The effect of bystander CPR and arrival time of EMS on successful out of hospital resuscitation. *Am J Emerg Med* 1984;2:358-359.

28. Bergner L, Eisenberg MS, Hallstrom A, et al: Evaluation of Paramedic Services for Cardiac Arrest: National Center for Health Services Research Report HS 02456. Washington, DC, Department of Health and Human Services, 1981.

29. American Heart Association: Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). *JAMA* 1980;244:453-509.

30. Bircher NG, Safar P: Cerebral preservation during cardiopulmonary resuscitation. *Crit Care Med* 1985;13:185-190.

31. Lowenstein SR, Hansbrough JF, Libby LS, et al: Cardiopulmonary resuscitation by medical and surgical house-officers. *Lancet* 1981;2:679-681.

32. Friesen L, Stotts NA: Retention of basic cardiac life support content: The effect of two teaching methods. *J Nurs Ed* 1984;23:184-191.

33. Babbs CF, Voorhees WD, Fitzgerald KR, et al: Relationship of blood pressure and flow during CPR to chest compression amplitude: Evidence for an effective compression threshold. *Ann Emerg Med* 1983;12:527-532.

34. Taylor GJ, Tucker WM, Greene HL, et al: Importance of prolonged compression during cardiopulmonary resuscitation in man. *N Engl J Med* 1977;296:1515-1517.

35. Rudikoff MT, Maughan WL, Effron M, et al: Mechanisms of blood flow during cardiopulmonary resuscitation. *Circulation* 1980;61:345-352.

36. Koehler RC, Chandra N, Guerci AD, et al: Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. *Circulation* 1983;67:266-275.

37. Koehler RC, Michael JR, Guerci AD, et al: Beneficial effect of epinephrine infusion on cerebral and myocardial blood flows during CPR. *Ann Emerg Med* 1985;14:744-749.

38. Bircher N, Safar P: Comparison of standard and "new" closed-chest CPR and open-chest CPR in dogs. *Crit Care Med* 1981;9:384-385.

39. Niemann JT, Rosborough JP, Niskanen RA, et al: Mechanical "cough" cardiopulmonary resuscitation during cardiac arrest in dogs. *Am J Cardiol* 1985;55:199-204.

40. Voorhees WD, Niebauer MJ, Babbs CF: Improved oxygen delivery during cardiopulmonary resuscitation with interposed abdominal compressions. *Ann Emerg Med* 1983;12:128-135.

41. Babbs CF: Preclinical studies of abdominal counterpulsation in CPR. *Ann Emerg Med* 1984;13:761-763.

42. Byrne D, Pass HI, Neely WA, et al: External versus internal cardiac massage in normal and chronically ischemic dogs. *Am Surgeon* 1980;46:657-662.

43. Stajduhar K, Safar P, Steinberg R, et al: Cerebral blood flow and common carotid artery blood flow during open-chest CPR in dogs. *Ann Emerg Med* 1984; 13:385.

44. Bircher NG, Safar P: Open chest CPR: An old method whose time has returned. *Am J Emerg Med* 1984;2:568-571.

45. Bircher N, Safar P: Manual open-chest cardiopulmonary resuscitation. *Ann Emerg Med* 1984;13:770-773.

46. Redding JS, Pearson JW: Evaluation of drugs for cardiac resuscitation. *Anesthesiology* 1963;24:203-207.

47. Michael JR, Guerci AD, Koehler RC, et al: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984;69:822-835.

48. Bleyaert AL, Nemoto EM, Safar P, et al: Thiopental amelioration of brain damage after global ischemia in monkeys. *Anesthesiology* 1978;49:390-398.

49. Goldstein A, Wells BA, Keats AS: Increased tolerance to cerebral anoxia by pentobarbital. *Arch Int Pharmacodyn* 1966;161:138-143.

50. Brann AW, Montalvo JM: Barbiturates and asphyxia. *Pediatr Clin North Am* 1970;17:851-862.

51. Smith AL, Hoff JT, Nielsen SL, et al: Barbiturate protection in acute focal cerebral ischemia. *Stroke* 1974;5:1-7.

52. Michenfelder JD, Milde JH, Sundt TM: Cerebral protection by barbiturate anesthesia. *Arch Neurol* 1976;33:345-350.

53. Nordstrom CH, Siesjo BK: Effects of phenobarbital in cerebral ischemia. Part I: Cerebral energy metabolism during pronounced incomplete ischemia. *Stroke* 1978;9:327-335.

54. Nordstrom CH, Rehncrona S, Siesjo BK: Effects of phenobarbital in cerebral ischemia: Part II: Restitution of cerebral energy state, as well as of glycolytic metabolites, citric acid cycle intermediates and associated amino acids after pronounced incomplete ischemia. *Stroke* 1978; 9:335-343.

55. Pulsinelli WA, Rawlinson D, Plum F, et al: Barbiturate exacerbation of ischemic brain damage following bilateral hemispheric ischemia in the rat. *Trans Am Neurol Soc* 1979;104:144-147.

56. Snyder BD, Ramirez-Lassepas M, Sukhum P, et al: Failure of thiopental to modify global anoxic injury. *Stroke* 1979;10:135-141.

57. Steen PA, Milde JH, Michenfelder JD: No barbiturate protection in a dog model of complete cerebral ischemia. *Ann Neurol* 1979;5:343-349.

58. Todd MM, Chadwick HS, Shapiro HM, et al: The neurological effects of thiopental therapy following experimental cardiac arrest in cats. *Anesthesiology* 1982;57:76-86.

59. Gisvold SE, Safar P, Hendricks HHL, et al: Thiopental treatment after global brain ischemia in pigtailed monkeys. *Anesthesiology* 1984;88-96.

60. Abramson N, Safar P, Detre K, et al: Brain resuscitation: Results of an international randomized clinical trial. *Am J Emerg Med* 1984;2:347.

61. Gergis SD, Sokoll MD, Sarracino SM, et al: Effect of Ca++ channel blocker on cerebral reflow phenomenon in the dog. *Anesthesiology* 1982;57[Suppl]:A363.

62. Vaagenes P, Cantadore R, Safar P, et al: The effect of lidoflazine and verapamil on neurological outcome after 10 minutes ventricular fibrillation cardiac arrest in dogs, abstract. *Crit Care Med* 1984; 12:228.

63. Hadorn DC: A small animal model of cerebral ischemia: Verapamil improves neurological outcome. *Ann Emerg Med* 1984;13:385-386.

64. White BC, Gadzinski DS, Hoehner PJ, et al: Effect of flunarizine on canine cerebral cortical blood flow and vascular resistance post cardiac arrest. *Ann Emerg Med* 1982;11:119-126.

65. Newberg LA, Steen PA, Milde JH, et al: Failure of flunarizine to improve cerebral blood flow or neurologic recovery in a canine model of complete cerebral ischemia. *Stroke* 1984;15:666-671.

66. Wauquier A, Edmunds HL, Melis W, et al: Flunarizine in the treatment of experimental canine cardiac arrest, abstract. *Am J Emerg Med* 1984;2:361.

67. Newberg LA, Steen PA, Gisvold SE, et al: Effects of nimodipine on neurologic function following complete global ischemia in primates. *Anesthesiology* 1984;61[Suppl]:A127.

68. Kovach AGB, Sandor P: Cerebral blood flow and brain function during hypotension and shock. *Ann Rev Physiol* 1976;38:571-596.

69. Winegar CP, Henderson O, White BC, et al: Early amelioration of neurologic deficit by lidoflazine after fifteen minutes of cardiopulmonary arrest in dogs. *Ann Emerg Med* 1983;12:471-477.

70. Lightfoote WE, Molinari GF, Chase TN: Modification of cerebral ischemic damage by anesthetics. *Stroke* 1977; 8:627-682.

71. Dean JM, Hoehner PJ, Rogers MC, et al: Effect of lidoflazine on cerebral blood flow following twelve minutes total cerebral ischemia. *Stroke* 1984;15:531-535.

72. Vaagenes P, Cantadore R, Safar P, et al: Amelioration of brain damage by lidoflazine after prolonged ventricular fibrillation cardiac arrest in dogs. *Crit Care Med* 1984;12:846-855.

American College of Emergency Physicians

PRESENTS **CREM III**

SURGERY-TRAUMA

November 15-19, 1985
Detroit, Michigan

At the completion of this program, the participant will be able to:

- Discuss priorities in the management of the critically injured
- Demonstrate suturing techniques for wound closure
- Demonstrate proper splinting and casting techniques
- Demonstrate proper procedures for using the slit lamp to remove foreign objects from the eye
- Discuss proper techniques for the initial treatment of burns

— An optional procedural skill station covering emergency invasive techniques also is available

All meetings and accommodations at the Detroit Westin Hotel
$72 — Single
$82 — Double

REGISTRATION FEES
$525 — ACEP Member
$575 — Physician Non-member
$210 — Optional Skill Station

For more information, contact ACEP, PO Box 619911, Dallas, Texas 75261-9911; 214 659-0911.

SPECIAL CONTRIBUTION
CT scanning, head trauma, intracranial hemorrhage, intracranial pressure

Advances in the Management of Closed Head Injury

The management of closed head injury has improved recently. Mortality rates for severe trauma are lower and outcomes are more favorable. Advances are related to improved diagnostic tools, such as computerized tomography scanning, aggressive supportive care, standardized evaluation criteria, and program-oriented rehabilitation. Further progress depends on sophisticated triage, including delivery of the patient to an experienced head-injury unit, as well as successful manipulation of cellular and subcellular processes to maintain brain homeostasis. Recent developments in the pathophysiology, diagnosis, and treatment of closed head injury are reviewed, and promising research avenues are discussed. [Lillehei KO, Hoff JT: Advances in the management of closed head injury. Ann Emerg Med August 1985;14:789-795.]

Kevin O Lillehei, MD
Julian T Hoff, MD
Ann Arbor, Michigan

From the Section of Neurosurgery, The University of Michigan, Ann Arbor, Michigan

Presented at the 1985 UAEM/RIEM Research Symposium in Orlando, Florida, February 7-8, 1985

This work was supported in part by a grant from the National Institutes of Health (NS 177601-5)

Address for reprints: Julian T Hoff, MD, C-5083 Outpatient Building, University of Michigan Hospitals, 1405 East Ann Street, Ann Arbor, Michigan 48109

Introduction

The management of closed head injury has improved during the past decade. Mortality rates for severe trauma are lower and outcomes are often more favorable. Awareness of the consequences of mild head injury also is better. These advances have come because the pathophysiology of head injury is better understood, because diagnostic tools are more accurate, and because treatment options are more specific. Worldwide efforts to standardize diagnostic criteria, to grade severity of injuries, and to assess outcome realistically also have contributed to improved care for head injury patients. Continued progress is primarily dependent on sophisticated triage and delivery of the patient to an experienced head-injury unit, as well as the use of rapid and accurate diagnostic tools. Further progress will result from more precise surgery, from the manipulation of cellular and subcellular processes to maintain brain homeostasis, from more reliable prediction of outcome, and from program-oriented rehabilitation.

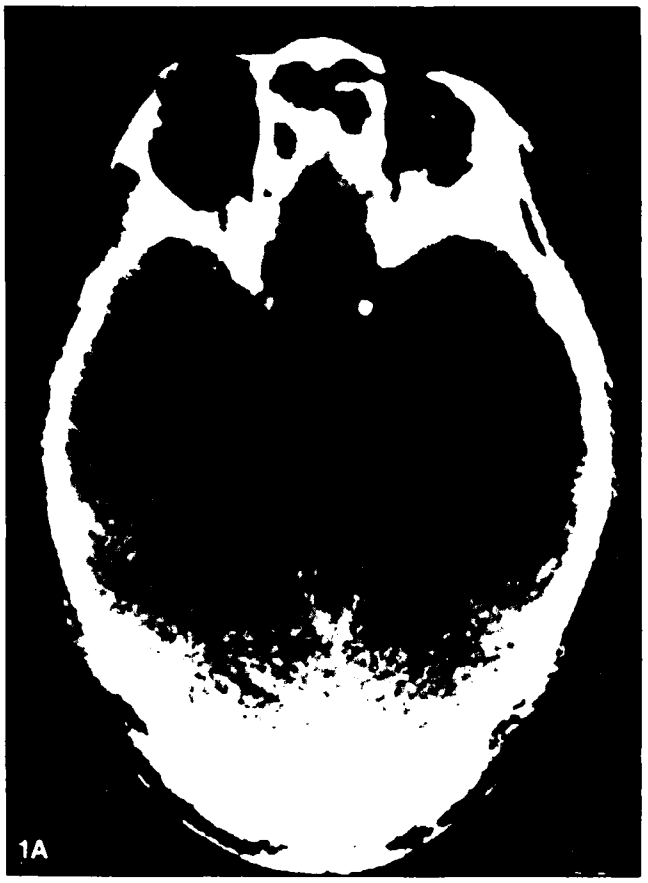
We review some advances in the pathophysiology, diagnosis, and treatment of closed head injury.

Pathophysiology

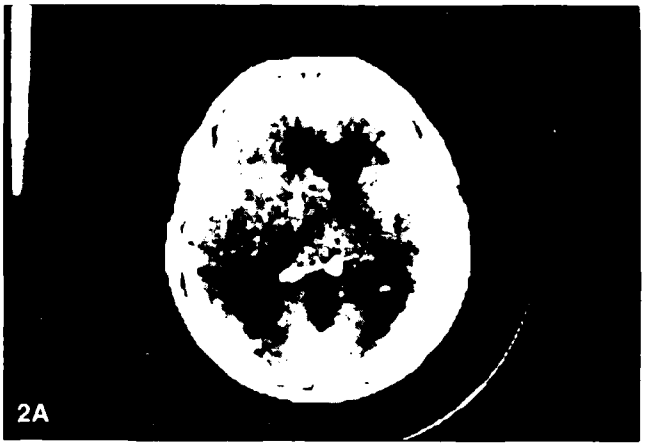
The brain in an average human adult weighs about 1,200 g and requires 15% of the total cardiac output. It functions almost entirely by oxidative metabolism and consumes 25% of the body's glucose, but it is unable to store oxygen or glucose to any significant degree. The neuron, therefore, depends on an uninterrupted blood supply for oxygen and glucose. To maintain this supply, the brain autoregulates its own blood flow to assure a continuous flow to brain tissue of about 50 to 60 mL/min/100 g. Deprivation of oxygen results in a shift to anaerobic metabolism, increased lactic acid, tissue acidosis, and cerebral vascular dilatation, all in an attempt to maintain homeostasis.[1] Disruption of the supply of oxygen or glucose to neurons, or alterations in the ability of neurons to utilize these substrates, results in physiologic dysfunction that may be reversible or irreversible.[2]

Two types of forces act on the brain at a time of impact: translational forces and rotational forces. All head injuries are a combination of these two forces; which force is predominant depends on the mode of injury. Brain structures are more susceptible to rotational forces, which can be devastating and are a fundamental cause of the classical "shearing" injury.[3,4]

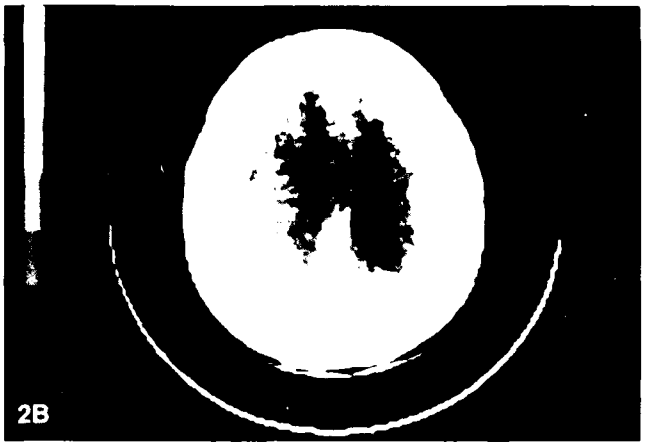
Focal brain injury typically is caused by translational forces. An example



1A



2A



2B

2C

Fig. 1. *CT brain scan, non-contrast-enhanced, 45-year-old woman. (A) Initial scan, 1½ hours after injury. Patient was stuporous, agitated, no focal signs. (B) Scan 14 hours after initial scan. Patient stuporous, agitated, mild left hemiparesis, slightly dilated right pupil. A large hematoma has formed in the right middle fossa. Prompt removal of the clot and intensive care resulted in complete recovery.*

Fig. 2. *Radiographic studies, 67-year-old man with headache, confusion, trivial head injury three weeks past. (A,B) CT brain scan, contrast enhanced. A shift of the ventricular system from left to right is evident, but no specific lesion can be seen. (C) Cerebral angiogram, AP view, same day as CT. The chronic isodense subdural hematoma accounting for the shift is seen (arrows).*

of a translational injury is cerebral contusion. This usually occurs at areas in direct contact with the irregular, inner surface of the calvarium, including the frontal poles, temporal poles, undersurface of the temporal lobes and, occasionally, the occipital poles.[1]

Epidural hematomas also are a result of translational forces, and are associated with an overlying skull fracture in 90% of cases. Approximately 50% to 60% of the time, epidural hematomas occur in the temporal region, where the fracture line crosses a branch of the middle meningeal artery. Unlike subdural hematomas, epidural hematomas are primarily arterial in origin, but they may be venous. Venous epidural hematomas occur secondary to disruption of a dural sinus or to prolonged venous oozing from a fracture site. Epidural hematomas are not usually associated with major underlying cerebral contusion and, if treated prior to secondary injury from mass effect, have an excellent prognosis.[1]

Rotational forces, unlike translational forces, usually cause more diffuse brain injury. Gennarelli recently described a spectrum of diffuse rotational brain injuries, characterizing each by the degree of irreversible anatomical disruption of neurons.[3] The least severe of these injuries is mild concussion, a temporary disturbance of neurologic function (ie, confusion or amnesia) without loss of consciousness. Next in severity is cerebral concussion associated with transient, reversible neurological dysfunction and temporary loss of consciousness (less than 24 hours). The third category is diffuse cerebral injury associated with prolonged loss of consciousness (24 hours), usually resulting in residual neurologic, psychologic, and personality deficits.

Fourth, and most severe, is the diffuse white matter shearing injury associated with anatomical disruption of axons throughout both cerebral hemispheres. This shearing injury is associated with high mortality and substantial residual neurologic morbidity. It results from rotational forces that are directed perpendicularly to the axis of the white matter and it results in axonal transection. Despite severe shearing injury, the brain may appear grossly normal; but numerous axonal transections can be seen microscopically in white matter within two weeks of injury and, classically, hemorrhage is present in the corpus callosum and cerebral peduncles. Wallerian degeneration subsequently occurs, with fiber tract demyelinization extending throughout the cerebral hemispheres and into the brain stem. Some degree of irreversible anatomic disruption probably occurs in all rotational injuries, and this may be the cause of persistent mild abnormalities now recognized by detailed psychometric testing of patients with mild concussions. Repeated insults with accumulation of these injuries may explain the progressive nature of the "punch drunk" syndrome.[4]

Posttraumatic brain swelling is the single most frequent cause of death of severely head-injured patients who reach the hospital. Brain swelling compromises oxygenation and glucose delivery to neurons, and may convert reversible physiologic dysfunction into irreversible injury. Control of brain swelling is important clinically, because treatment can directly affect outcome of patients with severe injuries.[5]

Posttraumatic brain swelling may be of the early- or late-onset variety. Early brain swelling is due to vascular engorgement resulting from impaired autoregulation. It results in hyperemia ("luxury perfusion"), despite depressed cortical electrical activity and oxygen consumption. The cause of early brain swelling from vascular engorgement is unclear, but it may be related to release of vasoactive materials from injured brain tissue or injury to vasomotor regions in the midbrain.[6] Use of osmotic diuretic agents such as mannitol may be detrimental to the treatment of this type of brain swelling, because intravascular volume is increased by the drug and swelling may be exaggerated.

Brain swelling that develops 24 to 48 hours (or more) after the injury is from cerebral edema. Posttraumatic edema is a combination of swelling in both the cellular (cytotoxic) and extracellular (vasogenic) compartments. This is a result of physiologic dysfunction with impaired integrity of the blood brain barrier. No specific treatment is available for posttraumatic brain edema.[7]

Diagnosis

The computerized tomographic (CT) scanner has had great impact on the diagnosis and treatment of head trauma.[8-10] Intracranial contusions, hematomas, and structural brain shifts can be identified reliably within minutes, and may be studied repeatedly thereafter with little risk to the patient. This enables the clinician to follow the evolution of the lesion precisely, and to assess its clinical relevance confidently. The capability to scan repeatedly has virtually eliminated the need for exploratory surgery which was done in the past to identify and remove intracranial hematomas. The use of arteriography to identify brain displacements and space-occupying masses has declined similarly. Thus the indications for and timing of surgery have changed, because the size, location, and behavior of a specific lesion, as well as its effect on surrounding structures, can be followed with relative ease. The type and timing of any surgical procedure then can be highly specific. In short, the CT scanner has changed the management of head injury dramatically. It, more than any other diagnostic or treatment factor, probably accounts for the improved results.

CT scanning of the head following trauma is usually performed initially without contrast enhancement. Bone detail, intracranial hemorrhage, brain shifts, ventricular size, and parenchymal anatomy are readily seen. Thus acute hematomas can be identified rapidly, and these data, together with the clinical status of the patient,

Fig. 3. *CT brain scan. Bone window. Same patient as in Figure 1. A basal skull fracture through the foramen magnum is shown (arrow).*

may be used to make intervention decisions (Figure 1).

Contrast enhancement during CT scanning is helpful after trauma if nonenhanced scans fail to identify a lesion. Older, isodense, liquefied intracranial hematomas are particularly difficult to see without radiopaque enhancement. Occasionally double-dose enhancement may reveal an otherwise invisible lesion. Arteriography is required if clinical suspicions for a space-occupying mass are high and CT images are nonspecific (Figure 2).

Computer manipulation of the radiographic image permits accurate delineation of skull fractures. The technique is particularly useful for basilar skull fractures, which may be seen in greater detail with CT than with traditional plain skull films (Figure 3). Consequently the use of plain films in the evaluation of head trauma is diminishing as the availability of CT increases.

Advances in the diagnosis and management of head injury are not limited to radiographic imaging. The severity of injury and the prognosis may be evaluated by serial analyses of somatosensory evoked potentials (SSEPs) and brain stem auditory evoked responses (BAERs). These tests of neural function supplement clinical examinations, and are most applicable to patients with severe injury and major neurological deficits.

Intracranial pressure (ICP) monitoring has become a standard tool in the management of severe head trauma. When ICP data, CT images, and the clinical status of the patient are combined and are followed carefully, diagnosis and treatment decisions become much less empirical. Although ICP is a good predictor of long-term outcome,[11,12] ICP data alone often do not correlate with specific lesions or predict clinical course. ICP monitoring does allow management decisions, including the use of osmotic diuresis, cerebrospinal fluid (CSF) drainage, and surgery, to be soundly based.[11,12]

Interest in that large pool of patients with minor head injury has increased recently. These patients usually have transient loss of consciousness after impact, have a brief period of amnesia, and have no focal neurologic signs. Careful neuropsychological follow-up has shown that many of these patients have prolonged cognitive and behavioral impairments.[4] Many also suffer from vocational maladjustment, poor concentration, headache, and dizziness for weeks or months after injury. Sophisticated psychological and social testing of patients with postconcussion syndrome now is routine in several head injury centers.

Treatment

Approximately 60,000 patients with severe head injury reach the hospital alive each year. This represents only half of those injured; the other half die before receiving hospital care. Of the patients who reach the hospital alive, about 25% have irreversible injury. The remaining 75% have some degree of reversible injury and may benefit from aggressive management. For example, about 50% of patients with severe head injury suffer from increased intracranial pressure, which can be controlled. Failure to control ICP is the single most frequent cause of death in hospitalized patients with severe head injury.[13]

Treatment of the head-injured patient is based on the prevention of secondary insults to the brain. The patient has a pool of reversibly injured neurons that are in tenuous circumstances. Any compromise in oxygenation or blood flow may tip this group of cells toward death. The goal of

TABLE. *Glasgow coma scale*

Eye Opening	
Spontaneous	E 4
To speech	3
To pain	2
Nil	1
Best Motor Response	
Obeys	M 6
Localizes	5
Withdraws	4
Abnormal flexion	3
Extensor response	2
Nil	1
Verbal Response	
Oriented	V 5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
Nil	1
Coma score (E + M + V) = 3 to 15	

treatment, therefore, is the prevention of the secondary insults that tip the balance.

Protective therapy should begin in the field.[14] These patients often demonstrate poor ventilation and may be hypotensive from associated injuries. Immediate controlled ventilation with support of oxygenation and circulation is crucial. When the patient reaches a hospital, an organized and experienced trauma team is essential for assessment of the patient's neurologic status as well as for identification of related injuries. If intracranial hypertension is suspected, controlled hyperventilation and osmotic diuretics are recommended during evaluation. Early recognition of intracranial lesions (subdural, epidural, or intracerebral hematomas) and prompt surgical decompression are vital. Whether or not a mass lesion is present, the patient should be managed in an intensive care unit (ICU) that is expert in the care of head injuries.[15]

When intracranial hypertension is suspected, ICP monitoring should be begun. The type of ICP monitor used depends on the individual patient. Ideally, intraventricular catheters are favored, both for reliability and for the ability to drain CSF when necessary. When a patient's ventricles are very small and difficult to penetrate, a subarachnoid bolt is preferred. ICP should be maintained at less than 20 mm Hg, primarily with the use of hyperventilation and osmotic diuretics.[16]

The role of nutrition in the severely head-injured patient remains controversial, but recent evidence suggests that early use of hyperalimentation may promote cerebral edema.[17] Nutritional support is usually begun within five to seven days following injury, when some recovery of the blood brain barrier can be expected.[18]

Standardization

Assessment of head injury severity and outcome has become standardized with the use of the Glasgow coma scale and the Glasgow outcome scales.[19,20] The Glasgow coma scale (GCS) is a 13-point scale divided into three categories of neurological responsiveness, and it has proved to be a reliable means of grading the severity of head injury (Table). Initial scoring is done after admission, and then scoring is repeated periodically. In the group of patients with a GCS score of 3 to 8, the prognosis at six months after injury is 48% mortality, 2% vegetative, 10% severe disability, 17% moderate disability, and 23% good recovery.[21] For the individual patient in this group Teasdale and Jennett found that advanced age, unreactive pupils, and decerebrate posturing all are predictors of poor outcome.[21]

The Glasgow outcome scale (GOS) is used to assess the neurologic outcome of patients months to years after injury, with emphasis on the patient's ability to function independently in society. The scale is divided into five categories: dead, vegetative, severely disabled, moderately disabled, and good recovery.

Use of the GCS and GOS provides a means to evaluate the effectiveness of current treatment regimens and new treatment regimens. These scales have permitted the creation of head injury data banks. The two largest are the Multicenter Head Injury Data Bank in the United States, funded by the National Institutes of Health, and the International Head Injury Data Bank, established in Great Britain. These banks provide a pool of control data against which new treatment protocols may be compared. They also provide a large pool of raw data for systematic investigation of head injury.

GCS and GOS prediction of outcome is based solely on early posttraumatic neurologic function, without consideration of the mechanism of injury. Employing a multicenter study, Gennarelli recently examined this aspect of head injury and divided the mechanism of injury into the following seven categories:[7] 1) focal injuries with extradural hematomas and surgery performed; 2) focal injuries with acute subdural hematomas and surgery performed; 3) other focal lesions with surgery performed; 4) other focal lesions, no surgery; 5) diffuse injuries with coma of six to 24 hours duration; 6) diffuse injuries with coma of greater than 24 hours duration and no decerebrate posturing; and 7) diffuse injuries with coma of greater than 24 hours duration and decerebrate posturing. In this study, the type of lesion was important to the ultimate outcome, independent of the GCS score. For example, patients having an acute subdural hematoma and a GCS score of 3 to 5 had a mortality of 74%; however, patients with a GCS score of 3 to 5 and diffuse injury and coma for six to 24 hours had a mortality of only 30%. Thus Gennerelli has shown that type of injury directly affects prognosis in patients having equivalent Glasgow coma scores.

The GCS and GOS also have been useful in evaluating moderate (GCS 9-12) and mild (GCS 12-15) head injuries. Rimel et al[22,23] demonstrated that patients with moderate head injury are older, are of a lower socioeconomic class, have a higher incidence of alcohol abuse, and have had previous head trauma more often than patients with mild injury. Patients with minor head injury in Rimel's study showed an unusually high incidence of complaints, with persistent headache (78%) and memory deficits (59%) reported three months after injury. One-third of those previously employed were unable to return to work.[22,23]

Future Treatments

The practical goals of head injury treatment have been, and will continue to be, preservation of brain homeostasis and prevention of second-

ary injury. All therapy is directed toward those ends, including removal of mass lesions, ventilation support, control of ICP, seizure prophylaxis, and maintenance of fluid, electrolyte, and nutritional balance. Prevention of secondary injury is the major focus of head trauma management. This follows the hypothesis that the primary insult initiates processes that may cause additional injury. Pathophysiological phenomena involved in complex head injury include regional (and sometimes global) ischemia, hypoxia, hemorrhage, blood brain barrier disruption, edema, CSF flow aberrations, neuronal and glial acidosis, and many others.[24,25]

Improvements in the mortality rate from severe head injury may be attributed to accurate and standardized clinical examinations, sequential CT studies, ICP monitoring, and aggressive intensive care. Advancements in monitoring that may further reduce mortality include regional cerebral blood flow determinations and the use of somatosensory and brain stem evoked responses to detect functional deterioration before it becomes clinically obvious.[26] In the future, high-resolution, rapid CT scanning may enable operative treatment to be more specific. Indications for surgery may change as lesions become better defined anatomically, and as their effects on function are more clearly understood.

The quest for protective therapy, both physiological and pharmacological, continues. During the past two decades, ICP control has been the focus of much basic and clinical research. Hyperventilation, hypothermia, osmotic diuresis, ventricular fluid drainage, and timely evacuation of space-occupying masses all have been helpful in maintaining ICP within physiologic ranges. Less research has been directed toward the more fundamental problems that occur with brain injury, such as parenchymal ischemia, hypoxia, and acidosis, all of which are involved in the clinical problem of brain swelling.

Since the early 1950s, steroids have been given to patients with head injury, yet neither clinical nor experimental evidence has emerged to justify the routine use of these drugs in the management of head trauma. In fact, many clinicians who treat head-injury patients believe that steroids contribute to complications seen often after trauma, including pneumonia and sepsis.[11,13,15]

Barbiturates reduce ICP because they depress blood flow, metabolism, and oxygen consumption. Although barbiturates protect against regional ischemia in certain experimental situations, these compounds have not proven to be effective clinically for stroke or for trauma-induced ischemia.[27,28] On the other hand, recent studies do show that large doses of barbiturate can control intracranial hypertension that is otherwise intractable.[29] The use of barbiturate coma has not had an appreciable effect on mortality rates or long-term morbidity.[15]

Tris (hydroxymethyl) aminomethane:tromethamine (THAM) has attracted interest as a treatment option for severe brain injury. It is promising because it is an excellent alkalinizing agent that is well tolerated systemically. The rationale for its use is based on the fact that tissue lactic acidosis, a consequence of ischemia, creates a harmful environment for brain cells. Experimentally in animals, THAM can improve outcome from closed head injury.[30] Human studies with this drug have just begun.

Interest in agents that reverse ischemia has been rekindled, because traumatized brain is ischemic to varying degrees. Calcium channel-blocking drugs such as nimodipine may prevent the ischemic change that accompanies cerebral vasospasm after subarachnoid hemorrhage.[31,32] Clinical studies indicate benefits in patients with ruptured aneurysms, but head-injury patients have not yet been treated systematically with this family of compounds.

Experiments with regional cerebral ischemia show variable success with dimethyl sulfoxide (DMSO),[11] naloxone,[33] thyrotropin-releasing hormone (TRH),[33] and fluosol,[34] the solvent that increases oxygen-carrying capacity. These drugs have not consistently altered outcome from severe head injury. Vascular volume control is also under investigation in patients with ischemia, but benefit has not yet been shown in head-injury patients.[35] It appears unlikely that a single drug or physiological manipulation will have much effect on the injured brain, because trauma involves many primary and secondary complex and interrelated events. No doubt the quest for the right combination to improve outcome will continue.

References

1. Jennett B, Teasdale G: *Management of Head Injuries*. Philadelphia, FA Davis, 1981, p 361.

2. Astrup J: Energy-requiring cell functions in the ischemic brain: Their cortical supply and possible inhibition in protective therapy. *J Neurosurg* 1982;56:482-497.

3. Gennarelli TA: Cerebral concussion and diffuse brain injuries, in Cooper PR (ed): *Head Injury*. Baltimore, Williams and Wilkins, 1982, pp 83-97.

4. Strich SJ: Diffuse degeneration of the cerebral white matter in severe dementia following head injury. *J Neurol Neurosurg Psychiatr* 1956;19:163-185.

5. Miller JD, Becker DP: General principles and pathophysiology of head injury, in Youmans JR (ed): *Neurological Surgery*. Philadelphia, WB Saunders, 1982, pp 1896-1937.

6. Bruce DA, Alavi A, Bilaniuk L, et al: Diffuse brain swelling following head injuries in children: The syndrome of "malignant brain edema." *J Neurosurg* 1981; 54:170-178.

7. Gennarelli TA, Spielman GM, Langfitt TW, et al: Influence of the type of intracranial lesion on outcome from severe head injury. *J Neurosurg* 1982;56:26-32.

8. Toutant SM, Klauber MR, Marshall LF, et al: Absent or compressed basal cisterns on first CT scan: Ominous predictors of outcome in severe head injury. *J Neurosurg* 1984;61:691-694.

9. VanDongen KJ, Braakman R, Gelpke GJ: The prognostic value of computerized tomography in comatose head-injured patients. *J Neurosurg* 1983;59:951-959.

10. Zimmerman RA, Bilaniuk LT, Gennarelli TA: Computed tomography of shearing injuries of the cerebral white matter. *Radiology* 1978;127:393-396.

11. Marshall LF, Bowers SA: Medical management of intracranial pressure, in Cooper PR (ed): *Head Injury*. Baltimore, Williams and Wilkins, 1982, pp 129-146.

12. Miller JD, Becker DP, Ward JD, et al: Significance of intracranial hypertension in severe head injury. *J Neurosurg* 1977; 47:503-516.

13. Marshall LF, Bowers SA: Medical management of head injury. *Clin Neurosurg* 1982;29:312-325.

14. Lokkeberg AR, Grimes RM: Assessing the influence of non-treatment variables in a study of outcome from severe head injuries. *J Neurosurg* 1984;61:254-262.

15. Becker DP, Miller JD, Ward JD, et al: The outcome from severe head injury with early diagnosis and intensive management. *J Neurosurg* 1977;47:491-502.

16. Saul TG, Ducker TB: Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. *J Neurosurg* 1982;56:498-503.

17. Waters D, Hoff J, Black K: Hyperosmolar nutritional support enhances vasogenic edema. *J Neurosurg*, in press.

18. Gadisseux P, Ward JD, Young HF, et al: Nutrition and the neurosurgical patient. *J Neurosurg* 1984;60:219-232.

19. Jennett B, Bond M: Assessment of outcome after severe brain damage. A practical scale. *Lancet* 1975;1:480-484.

20. Jennett B, Teasdale G, Braakman R, et al: Predicting outcome in individual patients after severe head injury. *Lancet* 1976;1:1031-1034.

21. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-84.

22. Rimel RW, Giordani B, Barth JT, et al: Disability caused by minor head injury. *Neurosurgery*, 1981;9:221-228.

23. Rimel RW, Giordani B, Barth JT, et al: Moderate head injury: Completing the clinical spectrum of brain trauma. *Neurosurgery* 1982;11:344-351.

24. Ljunggren B, Norberg K, Siesjo BK: Influence of tissue acidosis upon restitution of brain energy metabolism following total ischemia. *Brain Res* 1974;77: 173-186.

25. Rehncrona S, Rosen J, Siesjo BK: Excessive cellular acidosis: An important mechanism of neuronal damage in the brain? *Acta Physiol Scand* 1980;110: 435-437.

26. Bruce DA, Langfitt TW, Miller JD, et al: Regional cerebral blood flow, intracranial pressure, and brain metabolism in comatose patients. *J Neurosurg* 1973;38: 131-144.

27. Hoff J: Resuscitation in focal brain ischemia. *Crit Care Med J* 1978;6: 245-253.

28. Hossmann KA: Treatment of experimental cerebral ischemia. *J Cerebral Blood Flow and Metab* 1982;2:275-298.

29. Rea GL, Rockswold GL: Barbiturate therapy in uncontrolled intracranial hypertension. *Neurosurgery* 1983;12: 401-404.

30. Rosner MJ, Becker DP: Experimental brain injury: Successful therapy with the weak base, tromethamine. *J Neurosurg* 1984;60:961-971.

31. Allen GS, et al: Cerebral arterial spasm — A controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med* 1983;308:619-624.

32. Harris RJ, Branston NM, Symon L, et al: The effect of calcium antagonist, nimodipine, upon physiological responses of the cerebral vasculature and its possible influence upon focal cerebral ischemia. *Stroke* 1982;13:759-766.

33. Faden AI, Hallenbeck JM, Brown CQ: Treatment of experimental stroke: Comparison of naloxone and thyrotropin releasing hormone. *Neurology* 1982;32: 1083-1087.

34. Peerless SJ, Ishikawa R, Hunter G, et al: Protective effect of fluosol-DA in acute cerebral ischemia. *Stroke* 1981;12: 558-563.

35. Pritz MB, Giannotta SL, Kindt GW, et al: Treatment of patients with neurological deficits associated with cerebral vasospasm by intravascular volume expansion. *Neurosurgery* 1978;3:364-368.

Critical Decisions in Emergency Medicine

Sponsored by the American College of Emergency Physicians

AMERICAN COLLEGE OF EMERGENCY PHYSICIANS

A 12-Month Home-Study Subscription Series Approved for 24 Hours of ACEP and AMA Category I CME Credit

Critical Decisions in Emergency Medicine combines both audio and print in the premiere home-study program produced and sponsored by the American College of Emergency Physicians. This cost-effective method of CME provides you with concise updates in the latest developments in the field. It was developed with you in mind. You can study at your own convenience, at your own pace, with an easy-to-use cassette and study guide format. Each segment is written by experts in emergency medicine and provides practical clinical information.

☐ Edited by ACEP's home-study editorial board for accuracy and currency and based on needs identified by emergency physicians.

☐ CME credit for less than $8.00 per credit hour

The program content explores issues relevant to emergency care today, including:

■ *Headache:* Guidelines for Rapid Assessment—Gregory L. Henry, MD, FACEP

■ *Antibiotics:* Appropriate Selection in Emergencies—Eileen Hilton, MD

■ *Head Trauma:* Initial Management—Neal E. Little, MD, FACEP

■ *Prearrest Conditions:* Recognition in the Pediatric Patient—James H. McCrory, MD

■ *Communicable Diseases:* Prevention in Medical Personnel—P. Samuel Pegram, Jr, MD

■ *Suicidal Patients:* Rapid Risk Assessment—Douglas A. Rund, MD, FACEP

■ *Cardiovascular Drugs:* Recent Developments—David H. Cooke, MD

■ *Pneumatic Antishock Garments:* Concepts and Controversies—John B. McCabe, MD

■ *Cost Containment in Patient Care:* Steven Karas, Jr, MD

■ *Respiratory Emergencies:* Management in the Pediatric Patient—Martha Bushore, MD

■ *Abdominal Pain:* Differential Diagnosis in Children—Steven Ludwig, MD and Richard Ruddy, MD

■ *Cardiopulmonary Resuscitation:* Concepts and Controversies— James T. Niemann, MD

With the first month's program, subscribers will receive a convenient ring binder album to store cassettes and monographs. Then, each month for 12 months, subscribers will receive:

☐ An hour-long lecture on audiocassette

☐ A supplementary monograph

☐ A list of selected current readings

☐ A CME self-assessment test, with mailer.

The program provides subscribers with individual scores, CME test answers, and a certificate upon completion of CME credits.

SUBSCRIBE NOW!

Please enter my subscription to **Critical Decisions in Emergency Medicine**.
Make checks payable to:
Audio Visual Medical Marketing, Inc.
Dept. A
404 Park Avenue South, New York, NY 10016

Charge your order by phone, or for further information, call toll free: 1-800-221-3995. In New York State, call 1-212-532-9400

Name _____ Specialty _____
(please print)

Address _____

City _____ State _____ Zip _____

Fee: $175 Members $195 Nonmembers. This course is tax deductible. Price includes postage and handling. New York State residents add state and local taxes.

Please charge my [ ] Visa [ ] MasterCard Account no. _____ Expiration date _____

Session 4: Tissue Resuscitation

The portion of the UAEM/IRIEM Research Symposium on tissue resuscitation was primarily an extension of previous concerns, rather than a foray into new organ systems and their response to ischemia. The important (and neglected) topics of red cell substitutes and spinal cord injury were introduced, and we were given a brief glimpse into the extensive work and dedication of Dr Gould and Dr Anderson. The presentations on mitochondria and iron continue earlier discussions. To note that discussions on lung and renal effects were not part of the session is not to diminish the content or quality of the presentations, but rather to emphasize the vast scope of involvement emergency medicine must absorb when viewing resuscitation as a central focus for research. A summary statement of this last segment of the conference was that there is a need for a sincere commitment by a number of dedicated, intercommunicating scientists, supported with time and money by their clinical compatriots in the specialty. This need extends beyond the field of resuscitation to the many facets of medical research in which emergency medicine may have an impact. There is awareness of the need, but realization of progress has been slow.

Two important concepts were brought into focus by the discussions. First, reperfusion just "ain't what it used to be." Ischemic damage has been viewed as a "front-end" problem. In brain tissue, for example, there was a flow threshold (of both severity and duration) for reversible failure of neuronal function and one for irreversible membrane failure. Reperfusion brought one group of cells back and the others died. There was always a "zone of ischemia," where the ischemia penumbra reigned, and methods (eg, Sodi Polaris "salts") were touted to improve the fate of these undecided cells. Still, reperfusion was the key to salvation — that is, until the mid-1970s, when Safar's hypothesis on the damaging effects of reperfusion prompted increased concern about what our efforts to improve flow were doing.

The gap between time and severity of flow producing functional impairment and morphologic damage has taken on new meaning with studies of the posthypoperfusion syndrome or reperfusion injury mechanisms. The presentations of Dr White and Dr Fiskum support the concern that a little flow may be too much, and that "injury initiated during ischemia matures during reperfusion." The level of re-established flow initiating this maturation process and methods to block the cascade of events set in motion by ischemia are now the concern of resuscitation research. Dr White's work on calcium and iron, "a tale of two ions," typifies the continued evolution of our understanding, as early successes give way to nagging questions that underlie the complexity of the problem. In a summary of the past five to ten years of resuscitation, it was acknowledged that the threshold for cellular damage is not a specific flow value, but is a summation of the effects of residual flow values during ischemia; of the duration of ischemia; of the innate properties of individual tissues; of the timing, content, and degree of reperfusion flows; and of interventions that influence the processes set in motion by ischemia and developed through reperfusion. The rules of the game were revised once more for the clinicians in attendance.

The second concept brought into focus in the discussions was the ascendancy of the free radical as the intracellular villain of resuscitative efforts. Turnover in this position is rapid. Most recently it was held by arachidonic acid, for its multiple, detrimental effects in platelet aggregation, smooth muscle vasospasm, and membrane permeability. As pointed out by Dr Anderson, concerns about the influence of postischemic free radical development have been around for some time, but the combined presentation of Dr Anderson and Dr White, as well as other participants in the conference, placed "free radicals" as a central item of concern. A free radical is a molecule with a single, unpaired electron which may act as an oxidant or reductant. It is a by-product of a number of oxy-redox-related enzyme systems, and is eliminated through a ubiquitous enzyme pathway. Free radicals can initiate lipid peroxidation reactions that may result in lipid membrane loss, particularly in mitochondria. A transitional metal catalyst, such as iron, is needed for the initiation of lipid peroxidation. Given the finding of increased intracellular levels of free iron during ischemia, the free radical hypothesis takes on an important role in explaining its potentially damaging effects during and after ischemia. Free radicals also may be involved in xanthine oxidase activity and in direct injury in other tissues.

In the clinical correlation discussion, a number of projections for eventual applications of research were presented. Dr Gould noted that polymerized, pyridoxalated hemoglobin is a new development that may bring to fruition the extended promise of an effective red cell substitute. Its possible role as reperfusion fluid, and acknowledgment of the potential cellular hazards of the elevated free iron associated with a hemoglobin substitute, were discussed. It was recognized that, despite involvement in disaster management, prehospital care, and timely crossmatch problems, emergency medicine had little involvement in developing red cell substitutes. Dr Anderson's information on spinal cord injury could be applied directly to research on the early and optimal dosing of blockers of ischemic damage and reperfusion injury, such as methylprednisolone, naloxone, dimethyl sulfoxide (DMSO), thyrotropin-releasing hormone, and indomethacin. Dr White emphasized the need to establish resuscitative methods that provide maximum tissue perfusion; to avoid calcium use in resuscitation; and to develop clinical studies to support the

use of iron chelators and other methods to limit reperfusion injury by lipid peroxidation and other mechanisms.

The following political allegory is derived from this extremely enlightening session. The heart, brain, and other tissues have too long been viewed as separate entities in resuscitation research. Basic science teaches the interdependence of physiological and pathologic processes in maintaining or destroying the entire organism. As resuscitation research must expand its perspective to view the whole, so must clinical and academic emergency medicine work to maintain the specialty. The heart, brain, and other "peripheral tissue" must be considered in solving the problems confronting the organism, for organ isolation invites eventual death of the entire system.

Glenn C Hamilton, MD
Associate Professor of Emergency Medicine
and Internal Medicine
Wright State University School of Medicine
Dayton, Ohio

SPECIAL CONTRIBUTION
fluorocarbons; hemorrhagic shock;
oxygen transport; polyhemoglobin

Red Cell Substitutes: An Update

Steven A Gould, MD
Lakshman R Sehgal, PhD
Arthur L Rosen, PhD
Hansa L Sehgal
Gerald S Moss, MD
Chicago, Illinois

From the Department of Surgery, Michael Reese Hospital and Medical Center and the University of Chicago, Pritzker School of Medicine, Chicago, Illinois.

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985.

Supported in part by NIH Grant 5 RO1 HL30113-02.

Address for reprints: Steven A Gould, MD, Department of Surgery, Michael Reese Hospital and Medical Center, Lake Shore Drive at 31st Street, Chicago, Illinois 60616

The two acellular oxygen carriers currently being evaluated as red cell substitutes are hemoglobin solutions and fluorocarbon emulsions. We have shown that both products can maintain normal levels of oxygen consumption, CO_2 production, and circulatory dynamics in primates in the virtual absence of the red blood cell. Although each solution thus satisfies the most important criteria for a red cell substitute, development continues with both products. The clinical trials with the fluorocarbons have been discontinued due to the lack of efficacy of Fluosol-DA — 20% in the setting of acute blood loss. Our current hemoglobin preparation is a polymerized, pyridoxylated product that has a normal oxygen-carrying capacity. Clinical testing must await further evaluation of the safety and efficacy of this product. Alternative uses for both of these oxygen carriers continue to be explored, and may eventually be the area of their greatest utility in the clinical setting. [Gould SA, Sehgal LR, Rosen AL, Sehgal HL, Moss GS: Red cell substitutes: An update. Ann Emerg Med August 1985;14:798-803.]

RED CELL SUBSTITUTES

One of the exciting prospects for the future is the possibility of a safe and effective red cell substitute. The primary indication for such a product would be the unavailability of blood. The most important properties of a suitable red cell substitute should be the ability to effectively transport O_2 and CO_2 and to support circulatory dynamics. In addition, the preparation should be nontoxic and temperature stable, have a long shelf storage time and a suitable intravascular persistence, require no crossmatch before administration, and be effective on room air.

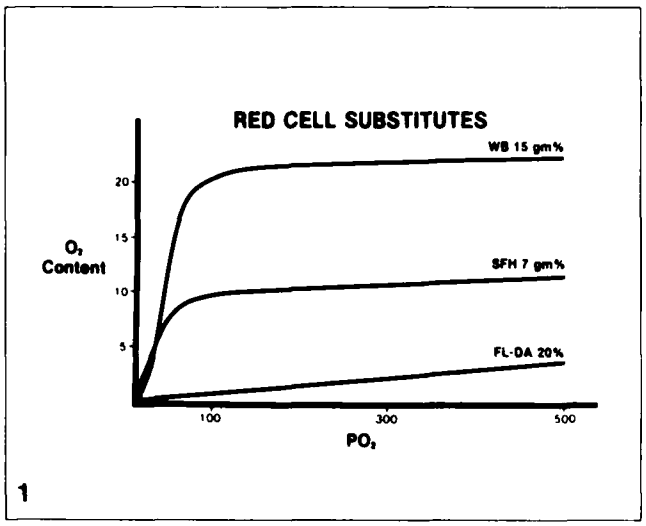
The two principal products currently being evaluated are hemoglobin solutions and fluorocarbon emulsions. We have shown that both products can maintain normal levels of O_2 consumption, CO_2 production, and circulatory dynamics in primates in the virtual absence of the red blood cell.[1-3] Although each solution therefore satisfies the most important criteria for a red cell substitute, certain problems exist in both instances that must be resolved prior to their clinical application.

HEMOGLOBIN SOLUTIONS

Unmodified Hemoglobin

Hemoglobin solutions are currently prepared from outdated blood. An important advance in the preparation of the solution was described in 1967 by Rabiner.[4] His technique of osmotic lysis, centrifugation, and filtration resulted in a stroma-free hemoglobin solution (SFH) with a [Hb] = 7 g/dL and an oncotic pressure (COP) equal to that of plasma. Our current approach to the preparation of "membrane-free" or stroma-free hemoglobin solution involves the gentle lysis of washed red cells with hypotonic phosphate buffer. Subsequent separation of the red cell "ghosts" from the hemoglobin is carried out by a series of filtration steps. The resultant hemoglobin solution is essentially free of red cell membrane or stromal contaminants. The properties of the final product are shown (Table 1).

The O_2 content curve of the SFH is both anemic and leftward-shifted in comparison to a 15 g/dL whole blood product (Figure 1). Although baboons can survive a total exchange transfusion with this SFH solution to zero hematocrit with normal levels of O_2 consumption, cardiac output, and arterio-



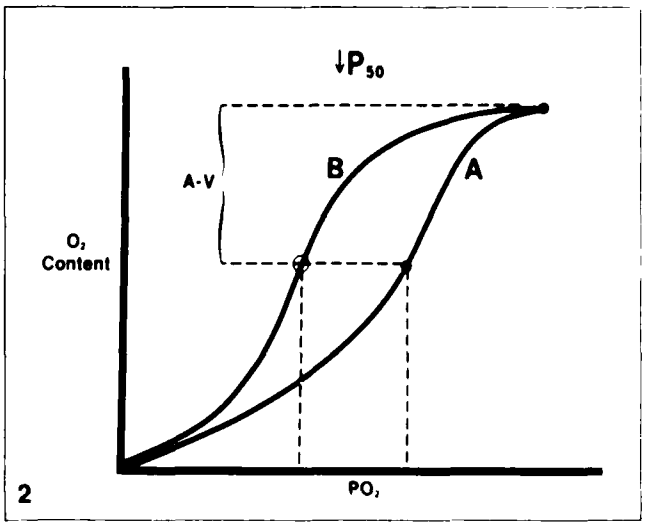


Fig. 1. *O_2 content curves for whole blood, SFH and FL-DA, 20%.*

Fig. 2. *Effect of a leftward shift in the oxygen content curve. Curve A is in the normal position. Curve B is shifted leftward. Assuming no change in A-VDO_2, the result must be a decline in the $P\bar{v}O_2$.*

venous O_2 content difference (A-VDO_2), a considerable decrease occurs in the mixed venous oxygen tension ($P\bar{v}O_2$) from roughly 50 to 20 torr.[5] The $P\bar{v}O_2$ is the tension at which oxygen unloads from the hemoglobin molecule, and is in equilibrium with the tissue PO_2. Such a low $P\bar{v}O_2$ was a concern to us, and led us to attempt to restore a more normal value.

Pyridoxylated Hemoglobin (SFH-P)

The factors that lower $P\bar{v}O_2$ include a decrease in cardiac output, arterial saturation, hemoglobin mass, or P_{50} (↑ affinity state), and an increase in oxygen consumption.[2] In reviewing our baboon data we could eliminate changes in oxygen consumption, arterial saturation, and cardiac output as possible explanations for the decline in $P\bar{v}O_2$. That left for further consideration changes in hemoglobin mass and affinity state. We examined affinity state changes first. The way in which a leftward shift in the content curve could produce a decrease in the tension at which oxygen unloading occurs — the PvO_2 — is shown (Figure 2).

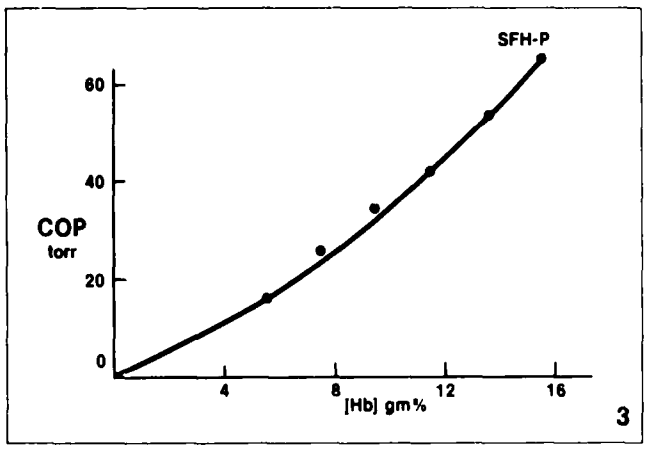
The increase in O_2 affinity state in the hemoglobin solution (↓ P_{50}) is related to the loss of the organic ligand 2,3-diphosphoglycerate (2,3-DPG), normally found within the red blood cell. Attempts to normalize P_{50} by the addition of 2,3-DPG to the hemoglobin solution itself were unsuccessful, for the DPG rapidly disappears from the circulation after infusion.[6] Benesch et al,[7] Greenberg et al,[8] and Sehgal et al[9] have described a modification of the hemoglobin molecule by the addition of pyridoxal-phosphate. The resulting compound, pyridoxylated hemoglobin (SFH-P) exhibits a P_{50} considerably higher than the P_{50} of unmodified hemoglobin. This modification allowed us to examine the PvO_2 in animals exchange transfused with pyridoxylated hemoglobin.[10]

Eight baboons were the test animals. Four received unmodified hemoglobin (P_{50} = 12 torr), while four received pyridoxylated hemoglobin (P_{50} = 22 torr). The exchange transfusion was carried out until zero hematocrit was achieved. The hemoglobin concentration of both solutions was approximately 7 g/dL. No important changes were noted following exchange transfusion in either group in oxygen consumption, cardiac output, or A-VDO_2. Animals that underwent exchange transfusion with SFH-P developed significantly higher whole blood P_{50} levels compared to those given unmodified hemoglobin (SFH) when the hematocrit levels declined to 10%. From this point onward, PvO_2 levels were significantly higher in the animals given pyridoxylated hemoglobin.[10]

These data illustrate two points. First, they confirm the concept that rightward shifts in the dissociation curve result in an increased PvO_2, as long as its other determinants remain constant, as was the case in this study (Figure 2). This is physiologically important, for it allows O_2 unloading to occur at a higher tissue PO_2. Second, although increased, the PvO_2 level (near 25 torr) in the animals treated with pyridoxylated hemoglobin was still substantially lower than the normal value of 40 to 50 torr found in control animals. Thus we began to search for other means to normalize the $P\bar{v}O_2$. Because [Hb] and P_{50} were the only two factors influencing PvO_2 that were changing, the remaining option was to raise the hemoglobin concentration of the SFH.

Polymerized Hemoglobin

One can easily prepare a hemoglobin solution with a normal hemoglobin concentration. Such a solution, however, has a colloid osmotic pressure in excess of 60 torr. The relationship between hemoglobin concentration and oncotic pressure is shown (Figure 3).[11] At hemoglobin concentrations of 7 g/dL, the oncotic pressure is similar to that of plasma — 20 torr. In contrast, at hemoglobin levels of 15 g/dL, oncotic pressure increases to greater than 60 torr. The infusion of such a solution might theoretically produce large fluid shifts from the extravascular to the intravascular space, a potentially harmful situation.



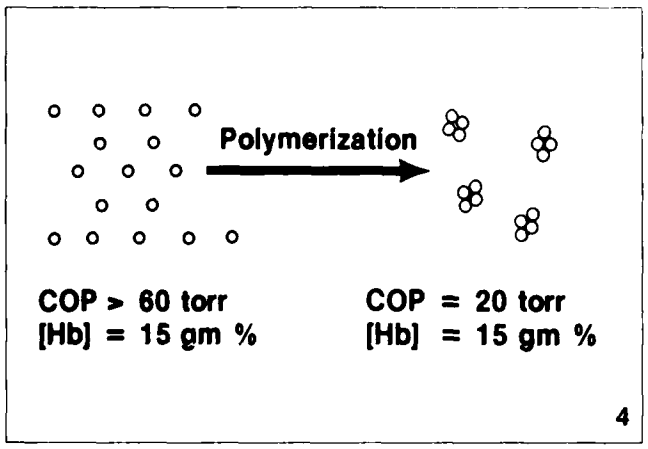


Fig. 3. *Relationship between colloid osmotic pressure (COP) and hemoglobin concentration ([Hb]) for pyridoxylated stroma-free hemoglobin (SFH-P).*

Fig. 4. *Polymerization results in a reduction in colloid osmotic pressure (COP) while maintaining a constant hemoglobin concentration ([Hb]).*

One approach to producing a nonanemic hemoglobin solution with normal COP values is polymerization of the hemoglobin molecule. The COP of any solution is proportional to the number of colloidal particles in the solution. If a 15-g/dL solution of hemoglobin could be polymerized, the result would be a reduction in the number of molecules and thus the COP, while no change would occur in hemoglobin concentration (Figure 4). We have successfully prepared such a product in large volumes.[12] The characteristics of such a polymerized pyridoxylated solution (poly SFH-P) are shown (Table 2).

Two kinds of preliminary studies have been carried out thus far. The first was to test the efficacy of the polyhemoglobin in rats. Eight rats were divided into two groups of four each.[13] The first group underwent total exchange transfusion with polyhemoglobin. The second group received 5% albumin solution. All the control rats died as the hematocrit declined to approximately 5%. All the rats given polyhemoglobin survived. These efficacy studies are now being repeated in baboons.

The second study concerned polyhemoglobin half-life.[14] Previous reports have demonstrated a relatively short half-life of tetrameric hemoglobin of approximately two to four hours. Much of the tetramer is cleared by the kidneys, following dissociation into dimers. The half-life of the polyhemoglobin was tested by infusion of 900 mL into adult baboons. Pyridoxylated hemoglobin served as the control solution. The polyhemoglobin shows a striking increase in half-life to 38 hours, compared to about four hours for pyridoxylated hemoglobin.

Future

Although we are encouraged at the prospects of this chemically modified polyhemoglobin solution serving as a temporary red cell substitute, the issue of toxicity is unresolved. There has always been concern over the possible nephrotoxic effect of free hemoglobin. A review of the literature reveals that evaluation of "pure" SFH in laboratory animals shows no abnormalities;[15] however, a recent report of SFH given to human volunteers did identify transient but reversible changes in renal function.[16] The issue is still not resolved. A second area of concern is postinfusion immunosuppression.[17,18] Because sepsis often follows hemorrhage and resuscitation, it is necessary to determine whether hemoglobin solution impairs the host defense mechanism. As modifications of the hemoglobin solutions are still in progress, a definitive answer must await a more detailed evaluation of the final polymerized hemoglobin solution.

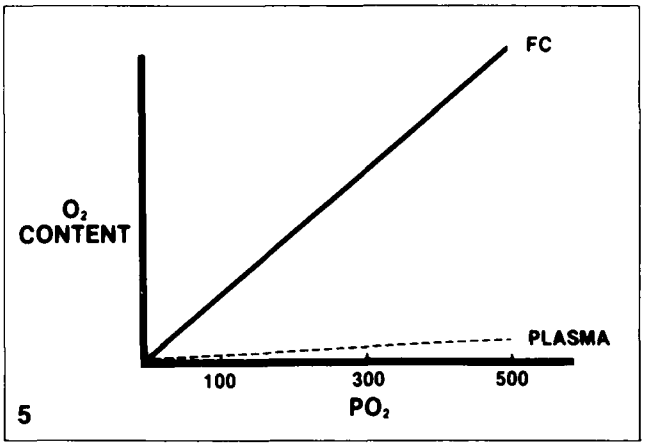
FLUOROCARBONS

Background

Fluorocarbons (FC) are fluorinated hydrocarbons that have a solubility for O_2 that is 10- to 20-fold greater than water (Figure 5).[2,3] Unlike the sigmoidal binding of O_2 to the hemoglobin molecule, the O_2 physically dissolved in the fluorocarbon phase is linearly related to the PO_2 (ie, the higher the PO_2, the more O_2 that is soluble). The slope of the line depends on the concentration of the FC and the solubility coefficient of the FC for O_2. Thus at any PO_2, the higher the FC concentration (or fluorocrit), the greater the O_2 content (Figure 6).

The commercially prepared perfluorochemical emulsion is Fluosol-DA, 20% (FL-DA). This product has been evaluated extensively in animals and human beings in Japan,[19,20] and recently underwent clinical testing in a number of institutions in the United States,[21] including our own trial at Michael Reese Hospital and Medical Center.[22]

A comparison of whole blood with a hemoglobin of 15 g/dL to FL-DA is shown (Figure 7). The figure illustrates that although the FL-DA does offer some value as an oxygen carrier, there are several limiting factors. First, the patient must breathe a high concentration of inspired oxygen in order to maximize the O_2 content of the FL-DA. Second, even at a PO_2 of 500 (breathing FiO_2 = 1.0), with the maximum achievable fluorocrit, the O_2 content is still less than 5 vol% compared to the 20 vol% seen with whole blood. The infusion of FL-DA would therefore add very little to the total O_2 content unless the [Hb] were considerably reduced from normal. The point of this observation is that although a potential benefit of FL-DA does exist, there are some significant



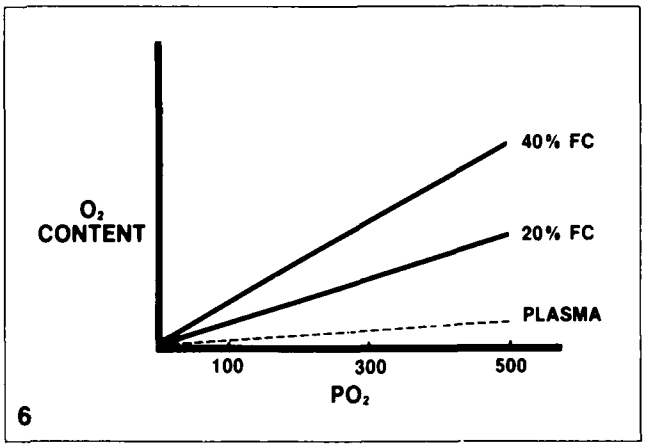


Fig. 5. *O_2 content curves for pure fluorocarbon and plasma.*

Fig. 6. *O_2 content curves for 40% fluorocarbon, 20% fluorocarbon, and plasma.*

limitations. Furthermore, the restrictions on the amount of FL-DA that can be administered to any patient (40 cc/kg) limits the achievable fluorocrit, which will further decrease the amount of oxygen that can be carried by the FL-DA (Figure 6).

Laboratory Studies

Our initial effort was to answer the question: How good are fluorocarbon emulsions as oxygen carriers? Because the principal requirement of any O_2 carrier is the ability to load and unload oxygen, it is necessary to accurately evaluate these functions. We have shown that adult baboons can survive a total exchange transfusion to zero hematocrit with FL-DA, if they are ventilated at an FiO_2 of 1.0.[23,24] The animals maintain normal hemodynamics and oxygen transport in the virtual absence of red blood cells. Although these data suggest that FL-DA is an effective oxygen carrier, we also demonstrated that control animals survive at zero hematocrit on an FiO_2 of 1.0 without FL-DA.[25] This observation leads to the conclusion that FL-DA is not necessary at FiO_2 of 1.0, at least in this acute setting.

These results can be explained by an understanding of the way in which the fluorocarbons carry oxygen. In the presence of red blood cells and FC, the total oxygen content in the blood can be considered the sum of three separate oxygen carriers:

$$[O_2]_{Total} = [O_2]_{RBC} + [O_2]_{Plasma} + [O_2]_{FC}$$

Survival depends on total oxygen content, but does not distinguish between each of the oxygen carriers.[1,26] The important observation is that at a PO_2 of 500 torr the plasma becomes a very significant carrier of oxygen that is capable of supporting oxygen consumption even in the complete absence of both RBC and FC. Because the $[O_2]_{PL}$ will always be increased at FiO_2 of 1.0, the actual need for the FL-DA is unclear.

Although this study documents the efficacy of the plasma as an oxygen carrier at FiO_2 of 1.0, we are concerned about the potential risk of oxygen toxicity to the lungs in the clinical setting.[27] The safe level of supplemental oxygen is thought to be an FiO_2 < 0.6. Although our data suggest that FL-DA might not be necessary at FiO_2 of 1.0, we cannot assume that the same situation would be true at lower levels of supplemental oxygen.

Clinical Trial

The results of our animal study led us to design our clinical trial to evaluate the safety and efficacy of FL-DA as an oxygen carrier. We sought to try to distinguish between the contribution of the dissolved oxygen in the plasma and the dissolved oxygen in the FL-DA compartment. Further, we wanted to minimize the risk of toxicity from breathing 100% oxygen. The objective was therefore to provide sufficient O_2 delivery with FL-DA at FiO_2 < 0.6. Unlike most clinical trials, the protocol for FL-DA was nonblinded, and had a cross-over design, with each patient serving as his own control for each O_2 carrier. Such a design let us define the physiologic need for, and evaluate the efficacy of, FL-DA in acute anemia.

TABLE 1. *SFH properties*

[Hb]	7-8 g/dL
P_{50}	12-14 torr
COP	20-25 torr

TABLE 2. *Poly SFH-P properties*

[Hb]	14-16 g/dL
P_{50}	16-20 torr
COP	20-25 torr

Patients had to be at least 18 years old in order to be admitted into the study. Furthermore, the patient's arterial blood PO_2 (PaO_2) had to reach 300 torr or greater when receiving supplemental oxygen. Finally, the patient had to be normovolemic. The physiologic criteria of need derived from our control studies in baboons included: 1) [Hb] < 3.5 g/dL; 2) PvO_2 < 25 torr; and 3) O_2 extraction ratio (ER) > 50%.

A patient who met one of the inclusion criteria was first treated with 100% oxygen. An attempt was made to stabilize the patient's condition at the clinically safe inspired oxygen level of 60% by a gradual tapering pro-

cess. If successful, the patient was considered to have no physiologic need for an increased O_2 content, and did not receive FL-IDA. Inability to accomplish this goal resulted in the patient being crossed over to the FL-IDA treatment group. The patient then received FL-IDA up to a maximum permissible dose of 40 mL/kg of body weight. Once again, an attempt was made to stabilize the patient's condition at 60% oxygen with FL-IDA.

Goals

The study had three goals. The first was to identify a physiologic need for an additional oxygen carrier when the red cell compartment became inadequate, as defined by the physiologic criteria. The second goal was to attempt to increase the oxygen content using only the plasma as an oxygen carrier at a safe FiO_2. The third goal was to evaluate the FL-IDA as an oxygen carrier if the physiologic criteria of need still exist at an unsafe FiO_2.

Results

Data from the eight patients who have been treated are still being evaluated. In an effort to illustrate our findings to date, the important details for the first patient will be described.

The first patient was a trauma victim who had a hemoglobin concentration of 3.5 g/dL. He was given 100% oxygen according to the protocol. An attempt to lower the inspired oxygen concentration to 60% was unsuccessful. The patient then received six units (3 L) of FL-IDA. Following the FL-IDA infusion he was successfully stabilized at the clinically safe level of 60% oxygen. The short-term goal of the study was achieved.[27]

Outcome

The ideal outcome would have been for the FL-IDA to last until the patient's own red blood cells had regenerated so that the additional $[O_2]$ of the FL-IDA would no longer be necessary. This did not occur. The success of the FL-IDA was only temporary. There was a relatively rapid loss of FL-IDA from the circulation, and a very prolonged delay in the patient's red cell regeneration. Additional FL-IDA was given, up to the maximum dosage of 40 cc/kg. As long as FL-IDA was present in the circulation, the goals were achieved. After ten days, however, the total dose had been administered. There were complicated legal and ethical issues, and ultimately the patient received red cell transfusions following a court order. This resulted in his survival.

A number of additional patients have been treated with FL-IDA, and the findings were similar to those in the first patient. FL-IDA may be effective when a true physiological need is present, but its benefit is short-lived compared with the red cell regeneration time. Although the details are still being evaluated, the clinical trials have stopped for the present. It is unlikely that this first-generation product has a role in the treatment of acute blood loss. Products that have a higher FC concentration and a longer intravascular persistence may be more effective.

Conclusion

Both acellular oxygen carriers meet some of the criteria of an ideal red cell substitute. Both have shortcomings that may potentially be solvable.[28] Other areas of usage of these oxygen carriers are being explored, such as in the treatment of myocardial infarction[29] and stroke.[30] The rationale in these settings is that these alternative O_2 carriers may provide oxygen to areas of ischemia that red cells cannot reach due to the occlusive nature of the disease. In addition, both red cell substitutes may be useful as cardioplegia solutions and in organ preservation. Once the safety and efficacy of both carriers are established, other innovative uses may develop. Currently development of both products continues actively.

The Fluosol DA was provided by the Alpha Therapeutic Corporation, Los Angeles, California.

REFERENCES

1. Gould SA, Rosen AL, Sehgal LR, et al: Red cell substitutes. Hemoglobin solution or fluorocarbon? *J Trauma* 1982, 22:736-740.

2. Gould SA, Rice CL, Moss GS: The physiologic basis of the use of blood and blood products. *In* Nyhus LM (ed): *Surgery Annual*, vol 16. Connecticut, Appleton Century Crofts, 1984, pp 13-38.

3. Sehgal LR, Gould SA, Rosen AL, et al: Appraisal of red cell substitutes. Hemoglobin solution and perfluorochemical emulsions. *Lab Med* 1983;14:545-548.

4. Rabiner SF: Evaluation of a stroma free hemoglobin solution for use as a plasma expander. *J Exp Med* 1967;126:1127-1142.

5. Moss GS, DeWoskin R, Rosen AL, et al: Transport of oxygen and carbon dioxide by hemoglobin-saline solution in the red cell-free primate. *Surg Gynecol Obstet* 1976;142:357-362.

6. Sunder-Plassmann L, Dieterle R, Seifert J, et al: Stroma free haemoglobin solution as a blood replacement fluid. Actual state and problems. *Eur J Intensive Care Med* 1975;1:37-42.

7. Benesch RE, Benesch R, Renthal RD, et al: Affinity labeling of the polyphosphate binding site of hemoglobin. *Biochemistry* 1972;11:3576-3582.

8. Greenberg AG, Hayashi R, Siefert J, et al: Intravascular persistence and oxygen delivery of pyridoxylated stroma free hemoglobin during gradations of hypotension. *Surgery* 1979;86:13-16.

9. Sehgal L, Rosen A, Noud G, et al: Large volume preparation of pyridoxylated hemoglobin with high in vivo P_{50}. *J Surg Res* 1981;30:14-20.

10. Gould SA, Rosen A, Sehgal L, et al: The effect of altered hemoglobin-oxygen affinity on oxygen transport by hemoglobin solution. *J Surg Res* 1980;28:246-251.

11. Moss GS, Gould SA, Sehgal LR, et al: Hemoglobin solution — from tetramer to polymer. *Surgery* 1984;95:249-255.

12. Sehgal LR, Rosen AL, Gould SA, et al: Preparation and in vitro characteristics of polymerized pyridoxylated hemoglobin. *Transfusion* 1983;23:148-151.

13. Sehgal L, Rosen A, Gould S, et al: In vitro and in vivo characteristics of polymerized pyridoxylated hemoglobin solution; abstract 2383. *Fed Proc* 1980;39:718.

14. Sehgal LR, Gould SA, Rosen AL, et al: Polymerized pyridoxylated hemoglobin: A red cell substitute with normal O_2 capacity. *Surgery* 1984;95:433-438.

15. DeVenuto F, Friedman HI, Neville JR, et al: Appraisal of hemoglobin solution as a blood substitute. *Surg Gynecol Obstet* 1979;149:417-436.

16. Savitsky JP, Doczi J, Black J, et al: A clinical safety trial of stroma free hemoglobin. *J Clin Pharmacol Ther* 1978;23:73-80.

17. Hau T, Simmons RL: Mechanisms of the adjuvant effect of hemoglobin in experimental peritonitis. III. The influence of hemoglobin on phagocytosis and intracellular killing by human granulocytes. *Surgery* 1980;87:588-592.

18. Hoxt DB, Greenberg AG, Peskin GW, et al: Resuscitation with pyridoxylated stroma free hemoglobin: Tolerance to sepsis. *J Trauma* 1981;21:938-943.

19. Matsuno T, Ohyanagi H, Naito R,

Clinical studies of a perfluorochemical whole blood substitute (Fluosol-DA). *Ann Surg* 1982;195:60-69.

20. Naito R, Yokoyama K: *Perfluorochemical Blood Substitutes*. Osaka, Japan, The Green Cross Corp, 1978.

21. Tremper KK, Friedman AE, Levine EM, et al: The preoperative treatment of anemic patients with a perfluorochemical. *N Engl J Med* 1982;307: 277-283.

22. Gould SA, Rosen AI, Sehgal LR, et al: Clinical experience with Fluosol-DA, in Bolin RB, Geyer RP (eds): *Blood Substitutes*. New York, Alan R Liss Inc 1983, pp 331-342.

23. Gould SA, Rosen AL, Sehgal LR, et al: Oxygen transport with Fluosol-DA, 20%, abstract 2038. *Fed Proc* 1981;40:587.

24. Gould SA, Rosen AL, Sehgal LR, et al: Fluorocarbon emulsions: How good as oxygen carriers? *Surg Forum* 1981;23: 299-301.

25. Gould SA, Rosen AL, Sehgal LR, et al: Plasma: An alternative oxygen carrier? abstract 7864. *Fed Proc* 1982;41:1615.

26. Rosen AL, Sehgal LR, Gould SA, et al: Fluorocarbon emulsions: Methodology to assess efficacy. *Crit Care Med* 1982; 10:149-154.

27. Davis WB, Rennard SI, Bitterman PB, et al: Pulmonary oxygen toxicity. *N Engl J Med* 1983;309:878-883.

28. Gould SA, Rice CL, Moss GS: Which is the foreseeable clinical application of oxygen-carrying blood substitutes (fluorocarbon and hemoglobin solutions)? Which impact are they likely to have on the activity of blood services? *Vox Sanguinis* 1982;42:97-109.

29. Hirooka Y, Kudo H, Suzuki A: Effect of Fluosol-DA on experimental myocardial infarction, in *Proceedings IV International Symposium on Perfluorochemical Blood Substitutes*. Kyoto, Japan, Excerpta Medica, 1979, pp 285-305.

30. Peerless S, Ishikawa R, Hunter I, et al: Protective effect of Fluosol-DA in acute cerebral ischemia. *Stroke* 1981;12: 558-563.

SPECIAL CONTRIBUTION
iron; ischemia, brain, heart;
oxygen radicals; resuscitation

Postischemic Tissue Injury by Iron-Mediated Free Radical Lipid Peroxidation

Cell damage initiated during ischemia matures during reperfusion. Mechanisms involved during reperfusion include the effects of arachidonic acid and its oxidative products prostaglandins and leukotrienes, reperfusion tissue calcium overloading, and damage to membranes by lipid peroxidation. Lipid peroxidation occurs by oxygen radical mechanisms that require a metal with more than one ionic state (transitional metal) for catalysis. We have shown that cellular iron is delocalized from the large molecules where it is normally stored to smaller chemical species during postischemic reperfusion. Postischemic lipid peroxidation is inhibited by the iron chelator deferoxamine. Intervention in the reperfusion injury of membranes by chelation of transitional metals is a new and promising therapeutic possibility for protection of the heart and brain. [White BC, Krause GS, Aust SD, Eyster GE: Postischemic tissue injury by iron-mediated free radical lipid peroxidation. Ann Emerg Med August 1985;14:804-809.]

Blaine C White, MD*
Gary S Krause, MD*
Steven D Aust, PhD†
George E Eyster, VDM‡
East Lansing, Michigan

From the Section of Emergency Medicine, Department of Medicine,* and the Department of Biochemistry,† College of Human Medicine; and the College of Veterinary Medicine,‡ Michigan State University, East Lansing, Michigan

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985

Dr White and Dr Krause are supported in part by the Medical Research and Development Command of the United States Army. Dr Aust is supported in part by NIH Grant GM33443

Address for reprints: Blaine C White, MD, Section of Emergency Medicine, A-206 East Fee Hall, Michigan State University College of Human Medicine, East Lansing, Michigan 48824

Introduction

Initiation of cell damage during ischemia occurs as a result of oxygen depletion and the cessation of aerobic energy metabolism. Normal cellular chemistry in mammals involves precise, enzymatically controlled reactions supported by high adenosine triphosphate (ATP) levels in an oxygenated and mildly alkalotic environment. During ischemia, cellular chemistry does not cease; instead, its nature is shifted to reactions that occur in a reducing and acidotic environment, without oxygen or large amounts of ATP — reactions that may be neither supported nor controlled by enzymatic catalysis.

Resuscitation is an attempt to return the cell to its preischemic chemical environment; however, because resuscitation takes place in the face of chemical alterations that occurred during ischemia, reperfusion may result in rapid cell death. The primary goals of the study of resuscitation are identification of the ischemia-induced changes that may be lethal to cells, and development of physiologic and pharmacologic principles to control and reverse the consequences of ischemia.

Ischemia, Calcium, and Cell Death

One major factor that contributes to ischemic injury is cellular calcium overloading.[1] Calcium is vital to a number of physiological and biochemical processes, but the calcium ion is strictly compartmentalized by cells. Mammalian cells use energy-dependent pumps in the mitrochondria,[2] endoplasmic reticulum,[3] and plasma membrane[4] to maintain a 10,000/1 gradient of ionized calcium across the cell membrane. Upon depletion of ATP stores in early ischemia, the energy-dependent pumps can no longer function, and extra-cellular calcium equilibrates with the cytosol.[5,6] In the brain, ATP depletion and Ca^{2+} equilibrium is established within five minutes.[5] Early cellular calcium overloading also occurs with ischemia in the myocardium, although ATP depletion is somewhat slower.[6] Collapse of the mitochondrial chemosmotic gradient during ischemia causes these organelles to lose their sequestered Ca^{2+} to the cytoplasm.[1]

These shifts during complete ischemia occur between compartments; measurement of total tissue Ca^{2+} during complete ischemia reveals no in-

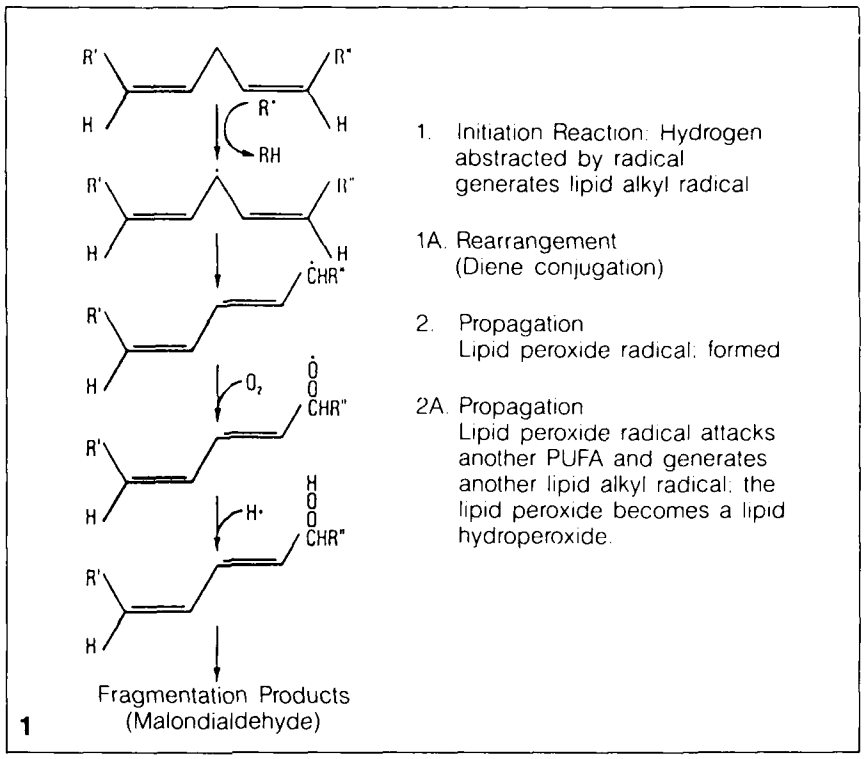


Fig 1. *Reaction sequence of a free radical (R) with a polyunsaturated fatty acid. These are the key reactions in the chain reaction of lipid peroxidation.*

crease. The consequences of this cellular calcium imbalance include activation of membrane-bound phospholipase[1,7] and conversion of xanthine dehydrogenase to xanthine oxidase.[8]

During reperfusion, calcium in the incoming plasma causes massive overloading of cells.[1] This has been demonstrated in the liver,[1] brain,[2] and heart,[10] and it probably occurs in most other organs as well. The result is substantial increases in total tissue calcium content, in contrast to the isolated compartmental shifts that occur during ischemia. Reperfusion Ca^{2+} overloading may be directly involved in cell death.[1] Indeed, liver cells can survive long ischemic periods or certain toxins usually associated with cell death if the extracellular fluid is low in Ca^{2+}.[1]

One result of calcium shifts during reperfusion after prolonged cardiac arrest is a progressive and prolonged increase in cerebral vascular resistance and a concomitant decrease in cerebral blood flow,[11-13] the delayed cerebral hypoperfusion syndrome. Although this syndrome may not be the proximate cause of postischemic brain cell death, it is probably a significant factor in postanoxic encephalopathy.

Following cardiac arrest lasting up to ten minutes, administration of calcium antagonists postischemia is effective in ameliorating hypoperfusion syndrome in the brain,[11-13] as well as total brain tissue calcium overload[9] and neurologic deficits.[14-16] Protection against reperfusion calcium overloading has not been seen with cardiac arrest times of 15 minutes or longer. Secondary Ca^{2+} overloading after prolonged ischemia in heart or liver cells may occur through direct increases in membrane permeability rather than through the normal calcium "channels."[1]

Several mechanisms have been suggested to account for the development of abnormal membrane permeability during prolonged ischemia and reperfusion. There is some evidence to suggest defective reacylation of membrane lipids with unsaturated fatty acids,[1,17] however, the significance of this remains unknown. A role for mechanical disruption of the membrane by Ca^{2+}-dependent contracture of cellular microtubules has been considered, although microtubular dismantling proved to be nonprotective in ischemia.[18] Peroxidation of membrane lipids initiated by oxygen radical species destroys lipid membranes in vitro[19] and could account for the increases in membrane permeability.

Reperfusion and Membrane Lipid Peroxidation

Injury initiated during ischemia matures during reperfusion. Reperfusion of the myocardium after prolonged regional ischemia results in rapid maturation of the injury to structurally obvious cell death.[20] This injury maturation is accompanied by the generation of malondialdehyde (MDA), a product of lipid peroxidation. Studies show that substantial amounts of myocardial tissue can be saved, and MDA production reduced, if superoxide dismutase is administered during reperfusion.[20] This enzyme converts the free radical superoxide (O_2^-) to hydrogen peroxide (H_2O_2). H_2O_2 can then be converted to water and oxygen by catalase, or to water by glutathione-peroxidase-catalyzed oxidation of glutathione.[21]

A free radical is a chemical with a single unpaired electron. Such molecules may act as reductants by transferring the unpaired electron to another chemical, or they may behave as oxidants by abstracting an electron from a chemical. Superoxide, the product of single electron reduction of molecular oxygen, is generated in normal metabolism by the mitochondrial cytochrome system, the mixed-function oxidases of the lysosomes (cytochrome P-450), and a number of other oxidative enzymes including cyclo-oxygenase, lipoxygenase, and xanthine oxidase.[22] Because of superoxide's potential for participation in non-enzymatically-regulated cellular redox reactions, several systems are available in the cell to eliminate this relatively ubiquitous radical species.[21] The mitochondria complete the reduction of superoxide to water by cytochrome oxidase. The superoxide dismutase/catalase/glutathione peroxidase system is found everywhere in the body. Vitamin E is intercalated in cell membranes, and serves as an electron donor to reduce radicals.

Lipid peroxidation takes place in a chain reaction. The three classic reactions of lipid peroxidation are initia-

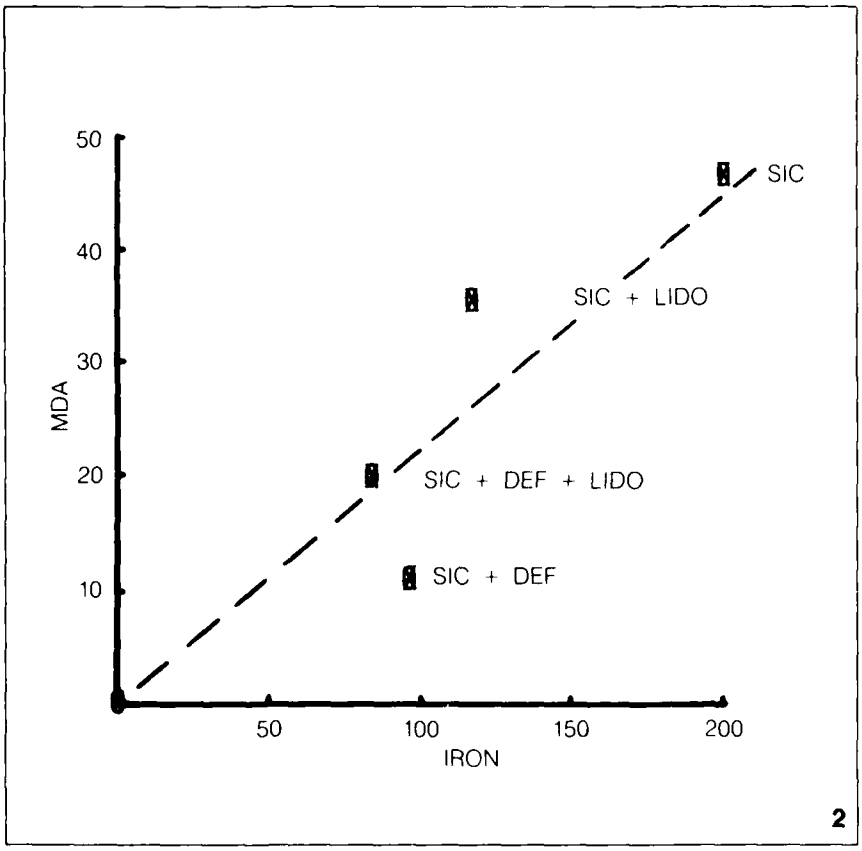


Fig 2. *Relationship of the changes in mean values of brain tissue low molecular weight iron species and of malondialdehyde. The zero point represents data from control animals that have not undergone cardiac arrest. The other four plotted points are from groups of five dogs each that all had 15-minute cardiac arrest and were resuscitated by internal cardiac massage. All brain tissue samples were taken for biochemical analysis two hours postresuscitation. All protective drugs were given by IV infusion during the first 15 minutes postresuscitation SIC = standard intensive care; DEF = deferoxamine; LIDO = lidoflazine.*

tion (Figure 1), propagation, and termination.[23] The first step, the initiation reaction, is the rate-limiting reaction. From the perspective of the potential for membrane protective therapy, the initiation reaction deserves special attention. Lipid peroxidation is initiated by oxidative abstraction of a divinyl hydrogen from a polyunsaturated fatty acid (PUFA) (Figure 1), thereby forming a lipid-alkyl free radical. The activation energy for this reaction is about 85 K Cal/mole.[24] This hydrogen requires less energy to remove than that in saturated carbon chains; indeed, saturated fatty acids do not readily undergo peroxidation reactions.

Propagation is a two-step process. First, the new lipid-alkyl free radical reacts with O_2 to form a lipid-peroxy radical:

$$L^{\cdot} + O_2 \rightarrow LOO^{\cdot}$$

Then, this lipid-peroxy radical can attack a divinyl hydrogen in an adjacent PUFA:

$$LOO^{\cdot} + LH \rightarrow L^{\cdot} + LOOH$$

In this reaction, the lipid-peroxy radical becomes a lipid hydroperoxide, and the PUFA it has attacked becomes a new lipid-alkyl radical. The chain reactions terminate when the lipid radicals react with each other to form stable products, or with scavenger molecules such as Vitamin E or sulfhydryl groups.[23]

The lipid hydroperoxides cross cell membranes, and may be found in the circulation.[19] In the presence of a transitional metal catalyst such as Fe^{2+}, they readily decompose to a lipid alkoxyl radical:[19]

$$Fe^{2+} + LOOH \rightarrow Fe^{3+} + OH^{-} + LO^{\cdot}$$

Thus the lipid hydroperoxides may initiate injury in organs other than the one that sustained the initial insult. Recognition of this may help us understand why studies of pharmacologic protection in models of isolated organ ischemia sometimes yield results that are more difficult to achieve when applied to the total body ischemia involved in cardiac arrest. This chemistry tends to substantiate the argument of Safar that post resuscitation encephalopathy may be a multiorgan syndrome in which other sick organs contribute to the pathology seen in the brain.[25]

Oxygen is intimately associated with propagation. The reaction between the lipid-alkyl free radical and O_2 is so rapid that termination is unlikely to occur.[23] Even at tissue O_2 levels of only 5% to 10% of normal, propagation will continue at about 50% of the maximum velocity.[26] In vitro studies of lipid peroxidation show that the optimum physical arrangement of PUFAs for propagation of lipid peroxidation is that of a closely packed monolayer.[19] Hence biological membranes are nearly an optimum environment for the chain reactions to continue.

Tissue and organelle susceptibility to lipid peroxidation is variable. Among tissues that have been studied, brain tissue has the highest rate of lipid peroxidation,[19] which is not surprising in view of the high content of PUFAs in the brain. Of the subcellular organelles, mitrochondria are particularly susceptible to lipid peroxidation.[19] Interestingly, these organelles demonstrate less loss of membrane lipids during ischemia than do other membranes in the cell.[1] Thus it is not surprising that brain mitochondrial injury during ischemia is minimal, while more severe injury occurs in certain marginal perfusion situations[27,28] or during in vitro induction of lipid peroxidation.[29]

Membrane Lipid Peroxidation and Iron

Thermodynamic studies of O_2 have shown that it has insufficient re-

activity to initiate lipid peroxidation. For the reaction between O_2^- and PUFA, the energy yield (ΔG) from abstraction of the divinyl hydrogen from the PUFA is +58 K Cal/mole.[30] Reduction of O_2^- to H_2O_2 has a ΔG of -18 K Cal/mole.[31] When the net ΔG of a reaction is positive, it is thermodynamically unfavorable. The sum of the ΔGs above is +40 K Cal/mole; thus direct initiation of lipid peroxidation by O_2^- is unlikely. Moreover, direct reaction between O_2 and the PUFA is spin-forbidden.[23] In the presence of a transitional metal catalyst such as iron, however, more reactive species are produced, and the spin restriction is overcome;[23] thus complexes involving oxygen and transitional metals can initiate lipid peroxidation.[23,32] Recent evidence that O_2^- releases iron directly from ferritin (by reduction of ferric to ferrous)[32] provides an alternative explanation for superoxide-mediated tissue injury and the protective effects of superoxide dismutase (SOD).

Initially it was thought that hydroxyl radical (OH·) was produced by a Haber-Weiss reaction between O_2^- and H_2O_2.[21] Strong evidence now indicates, however, that OH· is not the radical species involved in initiation of lipid peroxidation.[32,33] Rather, low molecular weight chelates (LMWC) of ferrous iron, such as ADP-Fe^{2+}, can undergo reactions with oxygen to generate active oxidation species, the chemical nature of which is not yet entirely clear.[33] Such iron-oxygen complexes can directly initiate lipid peroxidation in PUFAs.

There are, therefore, two critical questions in the study of postischemic membrane injury during reperfusion by lipid peroxidation through free radical mechanisms. First, does ferrous iron become available to catalyze lipid peroxidation during ischemia or reperfusion? Second, is there direct evidence that the products of lipid peroxidation can be found in tissue following ischemia and reperfusion?

The second question demands specific experiments that examine for the products of lipid peroxidation reactions. Initial attempts to investigate the role of free radicals in postischemic tissue injury used indirect studies of the detoxification systems instead of directly looking for the products of the reactions. For example, Siesjo et al[34] studied the glutathione peroxidase system in the postischemic brain and were unable to find changes in the ratio of reduced glutathione to oxidized glutathione. They concluded that this was evidence against free radical involvement in the pathology of brain ischemia and reperfusion. Kogure et al[35] recently demonstrated, however, that there was no change in glutathione ratios during 60 minutes of clearly documented lipid peroxidation in a minced brain preparation.

Iron is ubiquitous in mammalian tissue.[36] The heart contains 96 ± 35 μm iron per gram tissue ash, and the brain contains 63 ± 24 μm iron per gram tissue ash. The iron content in the brain is relatively uniform throughout the various substructures, except in the putamen and nucleus niger, where the content is two to three times higher.[37] Normally most of this iron is tightly bound in enzymes or stored in the ferric form in ferritin.

It appears that iron may be delocalized from normal sites within the cell during ischemia and reperfusion. Iron appears in an "unusual ligand field" in left ventricular tissue within 15 minutes of regional myocardial ischemia.[38] This is accompanied by increased MDA in left ventricular tissue after 45 minutes of ischemia.[38] Artman et al[39] have shown that infusion of small amounts of Fe^{2+} results in depression of the maximum rate of myocardial tension development and prolonged myofibrillar relaxation times. Protection from these effects was achieved with SOD but not with mannitol, an OH· scavenger.[21,23,29] These authors suggest that the Fe^{2+}-induced injury is dependent on formation of activated oxygen species, and that the prolonged relaxation time is evidence of a radical-induced defect in membrane calcium handling.

Studies in our laboratories demonstrate that myocardial tissue levels of low molecular weight chelate forms of iron are increased 40% after two hours of regional ischemia, and that MDA is also significantly increased.[40] Watson et al[41] have demonstrated that PUFAs containing conjugated diene bonds formed during lipid peroxidation[23] are increased in the postischemic brain. Although statistical analysis was not provided in this study, we have examined these data utilizing the independent two samples test of proportions. By this method, the increase in conjugated dienes is significant ($P < .001$).

We have reported that LMWC iron is increased three-fold in the brains of dogs after two hours of reperfusion following resuscitation from a 15-minute cardiac arrest (Figure 2).[42] This is accompanied by a 30% increase in brain tissue MDA levels, which is prevented by treatment with the iron chelator deferoxamine during reperfusion. Iron bound in the ferrioxamine complex is chemically inert, and iron-dependent lipid peroxidation cannot occur in the presence of stochiometrically adequate amounts of deferoxamine.[43]

Treatment with the calcium antagonist lidoflazine also significantly reduces the tissue LMWC iron levels.[42] In our experiments, the best reduction of tissue LMWC iron levels was obtained by postischemic treatment with both deferoxamine and lidoflazine. Babbs[44] has demonstrated a 100% increase in long-term survival and normal neurologic outcome in rats treated with deferoxamine after resuscitation from a ten-minute cardiac arrest.

Ferritin is a likely (but unproven) source for the iron released as a consequence of ischemia. The basic mechanism for the release of iron from ferritin is the reduction of the storage form of insoluble ferric iron (Fe^{3+}) to the ferrous (Fe^{2+}) state.[45] It is not surprising, therefore, that the reducing environment that develops in the cell during ischemia should be associated with increasing cellular concentrations of LMWC iron. Indeed, rapid release of iron from ferritin is observed in anaerobic conditions and is mediated by reduced $FMNH_2$.[45] FMN appears to be commonly associated with ferritin, and may be reduced by either NADH or NADPH.[45] The accumulation of NADH during ischemia is well documented,[46] and it occurs concomitantly with the accumulation of lactic acid.

Additional iron release from ferritin may be expected during reperfusion. The calcium-dependent transformation of xanthine dehydrogenase to xanthine oxidase[8] and the accumulation of hypoxanthine (a degradation product of ATP) during ischemia[47] results in the production of O_2^- by this enzyme during reperfusion.[48] Release of iron from ferritin is directly caused by O_2^- through reduction of the metal to the ferrous state:[32]

$$Fe^{3+} + O_2^- \rightarrow \text{free } Fe^{2+} + O_2$$

Treatment with allopurinol (an inhibitor of xanthine oxidase) during reperfusion protects postischemic bowel[48] and myocardium.[49]

Clinical Implications

Reperfusion following cardiac arrest should be accomplished by methods that provide optimum cardiac output and tissue perfusion, so that the reducing equivalents accumulated during ischemia are removed as rapidly as possible. This means that open-chest cardiac massage, which is significantly superior to closed-chest CPR for perfusing the heart and brain,[50] should yield improved resuscitation rates and neurologic outcome in patients, as it has in the laboratory.[50] These data are consistent with the observation of exacerbated lactic acidosis and tissue and mitochondrial injury in the brain when it is subjected to "trickle" blood flow rates commonly obtained with CPR.[27,28,50]

The data argue against the administration of calcium during resuscitation. They also suggest that the promising results for protection of the *postischemic brain* by calcium antagonists will not realize full clinical potential unless specific therapy is directed against reperfusion membrane injury by lipid peroxidation. Deferoxamine is a clinically available pharmaceutical with well-established administration guidelines and it has a history of being a safe drug.[51]

Chemically, the approach of stopping the initiation reaction of lipid peroxidation, and inhibiting the generation of lipid alkoxyl radicals from lipid hydroperoxides by controlling the iron, is attractive. This may be more promising than either hoping that scavengers (such as mannitol or vitamin E) can break up chain reactions by chemical competition in the tightly packed lipids of membranes, or attempting to intercept oxygen radicals after they are formed with scavenger enzymes (such as SOD). Moreover, although deferoxamine penetrates cells and the blood-brain barrier well,[51] it remains to be shown that large protein species such as SOD or catalase can or will do so.

The data also suggest that exacerbated tissue injury and arrhythmias occurring during management of myocardial infarction by promotion of myocardial reperfusion[20,49] may be related to iron-dependent lipid peroxidation. Although more laboratory work remains to be done to complete the picture of injury by ischemia and reperfusion already developed, there is already evidence to justify controlled clinical trials of deferoxamine, or the combination of deferoxamine and calcium antagonists, for the amelioration of reperfusion injury in the heart and brain.

Conclusions

We have reviewed evidence that tissue injury during ischemia is a function of the shift of the cellular chemistry to an anoxic-reducing environment that is ATP-depleted. This results in the following: 1) collapse of the mitochondrial chemosmotic gradient; 2) degradation of adenine nucleotides; 3) compartmental shifts of calcium; 4) activation of calcium-dependent catabolic enzymes; 5) release of PUFAs from membranes; 6) defective reacylation of lipids; and 7) delocalization of iron from storage to LMWC forms.

If the ischemia is prolonged and these processes are sufficiently developed, reperfusion results in formation of O_2^- and iron-dependent lipid peroxidation with loss of integrity in the plasma and mitrochondrial membranes. Then massive overloading of cells with calcium occurs, and the cells undergo coagulative necrosis. Lipid peroxidation and continuing iron delocalization are inhibited by treatment with the iron chelator deferoxamine. Calcium antagonists promote postischemic reperfusion. Continued studies of combination therapy with deferoxamine and calcium antagonists to protect the heart and brain during postischemic reperfusion are scientifically justified.

References

1. Farber JL: Membrane injury and calcium homeostatis in the pathogenesis of coagulative necrosis. *Lab Invest* 1982;47: 114-123.

2. Rossi CS, Lehninger AL: Stochiometry of respiratory stimulation: Accumulation of calcium and phosphate and oxidative phosphorylation in rat liver mitochondria. *J Biol Chem* 1964;239:3971-3980.

3. Madiera VMC: Proton movements across the membranes of sarcoplasmic reticulum during the uptake of Ca(2+). *Arch Biochem Biophys* 1980;200:319-325.

4. Dipolo R: Calcium pump driven by ATP in squid axons. *Nature* 1978;274: 390-392.

5. Harris RJ, Symon L, Bronston NM, et al: Changes in extracellular calcium activity in cerebral ischemia. *J Cereb Blood Flow Metab* 1981;1:203-209.

6. Katz AM, Reuter H: Cellular calcium and cardiac cell death. *Am J Cardiol* 1979;44:188-190.

7. Nemoto EM, Sjiu GK, Nemmer JP, et al: Free fatty acid accumulation in the pathogensis of cerebral ischemic-anoxic injury. *Am J Emerg Med* 1983;1:175-179.

8. Roy RS, McCord JM: Ischemia induced conversion of xanthine dehydrogenase to xanthine oxidase. *Fed Proc* 1982;41: 767-772.

9. De Garavilla L, Babbs CF, Borowitz JL: Effect of diltiazem on brain calcium content following ischemia and reperfusion in a rat circulatory arrest model, abstract. *Ann Emerg Med* 1984;13:385.

10. Shen AC, Jennings RB: Myocardial calcium and magnesium in acute ischemic injury. *Am J Pathol* 1972;67: 441-452.

11. Hoffmeister F, Kazda S, Krause HP: Influence of nimodipine on the post-ischemic changes of brain function. *Acta Neurol Scand* 1979;60(Suppl 72):358-359.

12. Steen PA, Newburg LA, Milde JH, et al: Nimodipine improves cerebral blood flow and neurologic recovery after complete cerebral ischemia in the dog. *J Cereb Blood Flow Metab* 1983;3:38-42.

13. White BC, Winegar CD, Wilson RF, et al: Calcium blockers in cerebral resuscitation. *J Trauma* 1983;23:788-793.

14. Winegar CP, Henderson O, White BC, et al: Early amelioration of neurologic deficit by lidoflazine after 15 minutes of cardiopulmonary arrest in dogs. *Ann Emerg Med* 1983;12:470-476.

15. Vaagenes P, Cantadore R, Safar P, et al: Amelioration of brain damage by lidoflazine after prolonged ventricular fibrillation cardiac arrest in dogs. *Crit Care Med* 1984;12:846-855.

16. Newburg LA: Cerebral resuscitation: Advances and controversies. *Ann Emerg Med* 1984;13(Part 2):853-856.

17. Chien KR, Reeves JP, Buja LM, et al: Phospholipid alterations in canine ischemic myocardium: Temporal and topographical correlations with Tc-99m-PPi accumulation and an in-vitro sarcolemmal calcium permeability defect. *Circ Res* 1981;48:711-717.

18. Okayasu T, Curtis MT, Farber JL: Cytochalasin delays but does not prevent cell death from anoxia. *Am J Pathol* 1984;117:163-166.

19. Mead JF: Free radical mechanisms of lipid damage and consequences for cellular membranes, in Pryor WA (ed): *Free Radical in Biology*. New York, Academic Press, 1976, pp 51-68.

20. Jolly SR, Kane WJ, Bailie MB, et al: Canine myocardial reperfusion injury. *Circ Res* 1984;54:277-284.

21. Brawn K, Fridovich I: Superoxide radical and superoxide dismutases: Threat and defence. *Acta Physiol Scand* 1980; 492(Suppl):9-18.

22. Freeman BA, Crapo JD: Free radicals and tissue injury. *J Lab Invest* 1982;47: 412-426.

23. Buege JA, Aust SD: Microsomal lipid peroxidation. *Methods in Enzymology* 1978;51:302-310.

24. Dahle LK, Hill EG, Holman RT: The thiobarbituric acid reactions and the autoxidations of poly-unsaturated fatty acid methyl esters. *Arch Biochem Biophys* 1962;98:253-261.

25. Safar P: Recent advances in cardiopulmonary-cerebral resuscitation: A review. *Ann Emerg Med* 1984;13(Part 2): 856-862.

26. Demopoulous HB, Flamm ES, Pietronigro DD, et al: The free radical pathology and the microcirculation in the major central nervous system disorders. *Acta Physiol Scand* 1980;492 (Suppl): 91-119.

27. Rehncrona A, Mela L, Siesjo BK: Recovery of brain mitochondria function in the rat after complete and incomplete cerebral ischemia. *Stroke* 1979;10:437-442.

28. White BC, Hildebrandt JE, Johns D, et al: Prolonged cardiac arrest and resuscitation in dogs: Brain mitochondrial function with different artificial perfusion methods. *Ann Emerg Med*. 1985, in press.

29. Hillered L, Ernster L: Respiratory activity of isolated rat brain mitochondria following in-vitro exposure to oxygen radicals. *J Cereb Blood Flow Metab* 1983;3:207-214.

30. Uri N: Physico-chemical aspects of autoxidation, Thermodynamics and activation energies, in Lundberg WO (ed): *Autoxidation and Antioxidants*. New York, Wiley Interscience, 1961, vol 1, pp 77-78.

31. Fee JA, DiCorleto PE: Observations on the oxidation-reduction properties of bovine erythrocyte superoxide dismutase. *Biochemistry* 1973;12:4893-4899.

32. Thomas CE, Morehouse LA, Aust SD: Ferritin and superoxide dependent lipid peroxidation. *J Biol Chem*. 1985, in press.

33. Gutteridge JMC: The role of superoxide and hydroxyl radicals in phospholipid peroxidation catalyzed by iron salts. *FEBS Lett* 1982;150:454-458.

34. Siesjo BK: Cell damage in the brain: A speculative synthesis. *J Cereb Blood Flow Metab* 1981;1:155-185.

35. Kogure K, Watson BD, Busto R: Potentiation of lipid peroxides by ischemia in rat brain. *Neurochem Res* 1982; 7:437-454.

36. Perry HM, Tipton IH, Schroeder HA, et al: Variability in the metal content of human organs. *J Lab Clin Med* 1962; 60:245-253.

37. Hocks A, Demmel U, Schicha H, et al: Trace element concentration in human brain. *Brain* 1975;98:49-64.

38. Rao PS, Cohen MV, Mueller HS: Production of free radicals and lipid peroxides in early myocardial ischemia. *J Mol Cell Cardiol* 1983;15:713-716.

39. Artman M, Olson RD, Boucek RJ, et al: Depression of contractility in isolated rabbit myocardium following exposure to iron: Role of free radicals. *Toxicol Appl Pharmacol* 1984;72:324-332.

40. Holt S, Gunderson M, Joyce K, et al: Myocardial tissue iron delocalization and evidence for lipid peroxidation after two hours of ischemia, abstract. *Ann Emerg Med* 1985;14:499.

41. Watson BD, Busto R, Goldberg WJ, et al: Lipid peroxidation in-vivo induced by reversible global ischemia in rat brain. *J Neurochem* 1984;42:268-274.

42. Nayini NR, White BC, Aust SD, et al: Post resuscitation iron delocalization and malondialdehyde production in the brain following prolonged cardiac arrest. *J Free Radicals in Biol Med*. 1985, in press.

43. Gutteridge JMC, Richmond R, Halliwel B: Inhibition of the iron-catalyzed formation of hydroxyl radicals from superoxide and lipid peroxidation by desferrioxamine. *Biochem J* 1979;184: 469-472.

44. Babbs CF: Role of iron ions in the genesis of reperfusion injury following successful cardiopulmonary resuscitation: Preliminary data and a biochemical hypothesis. *Ann Emerg Med* 1985;14:777-783.

45. Crichton RR: Interactions between iron metabolism and O_2 activation, in *Excerpta Medica*. New York, Ciba Foundation, 1979, vol 65, pp 57-72.

46. Ginsberg MD, Reivich M, Frank S: Pyridine nucleotide redox state and blood flow in the cerebral cortex following middle cerebral artery occlusion in the cat. *Stroke* 1976;7:125-131.

47. Thiringer K: Hypoxanthine as a measure of Foetal Asphyxia, doctoral, thesis, University of Goteborg, Goteborg, Sweden, 1982.

48. Parks DA, Bulkley GB, Granger DN, et al: Ischemic injury in the cat small intestine: Role of superoxide radicals. *Gastroenterology* 1982;82:9-15.

49. Myers C, Weiss SJ, Shepherd B, et al: Oxygen radical effects and defences in cardiac hypoxia or ischemia, in Aust SD (ed): *Great Lakes Workshop on Oxygen Radicals in Medicine and Biology*. East Lansing, Michigan State University, 1984.

50. Bircher N, Safar P: Open-chest CPR: An old method whose time has returned. *Am J Emerg Med* 1984;2:568-571.

51. Keberle H: The biochemistry of desferoxamine and its relation to iron metabolism. *Ann NY Acad Sci* 1974;119: 758-768.

52. Kloner RA, Ganote CE, Jennings RB: The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974;54:1496-1508.

SPECIAL CONTRIBUTION
ATP; brain; calcium; ischemia;
mitochondria

Mitochondrial Damage During Cerebral Ischemia

Cerebral ischemia causes a rapid decline in the ability of brain mitochondria to synthesize adenosine triphosphate when they are exposed to oxygen and oxidizable substrates. Ischemia also results in a decreased capacity for energized mitochondria to sequester the abnormally high levels of calcium that are present within ischemic tissue. The degree to which these processes are affected is likely to influence the maintenance of cell viability during cerebral resuscitation. Factors that have been proposed to account for mitochondrial damage during ischemia and reperfusion include intracellular acidosis, Ca^{2+}-induced membrane damage, and free-radical-dependent membrane lipid peroxidation. Ongoing research indicates that measures can be taken to manipulate these factors so that mitochondrial damage may be minimized and cell viability optimized during resuscitation. [Fiskum G: Mitochondrial damage during cerebral ischemia. Ann Emerg Med August 1985;14:810-815.]

Gary Fiskum, PhD
Washington, DC

From the Departments of Biochemistry and Emergency Medicine, The George Washington University School of Medicine, Washington, DC.

Presented at the 1985 UAEM/IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985.

Address for reprints: Gary Fiskum, PhD, Department of Biochemistry, The George Washington University School of Medicine, Washington, DC 20037.

Introduction

Continuous production of adenosine triphosphate (ATP) is required by all cells in order to remain alive. The energy needed to drive the synthesis of ATP from adenosine diphosphate (ADP) and inorganic phosphate (P_i) is derived primarily from the oxidation of nutrient substrates (eg, glucose) via metabolic pathways that require the presence of oxygen, and also from the anaerobic pathway of glycolysis (Figure 1).

Normally 80% to 90% of cellular ATP is generated from mitochondrial oxidative phosphorylation. Thus when the supply of O_2 to the tissue is interrupted (anoxia or complete ischemia) or drastically reduced (hypoxia or incomplete ischemia), the cell must rely on its reserves of high-energy phosphate bond energy (creatine phosphate) and glycolysis for the production of ATP. Even though the brain has a relatively high capacity for generating ATP from glycolysis, rapid utilization of ATP for the active transport of ions leads to complete depletion of ATP within a few minutes after the onset of severe incomplete or complete ischemia. Soon thereafter, degradative biochemical reactions initiate the process of cell death.

One key event that occurs when cellular ATP is depleted is an elevation of the intracellular Ca^{2+} concentration.[1] Without the ATP needed to transport Ca^{2+} out of the cell, it will rise from its basal cytosolic free concentration of approximately 0.1 μM and eventually equilibrate with the extracellular concentration of greater than 1.0 mM. This abnormal increase in intracellular Ca^{2+} activates a number of degradative enzymes such as phospholipases, which attack membrane lipids, and proteases, which inactivate enzymes as well as transport and structural proteins.

Reperfusion of ischemic tissue with O_2 and oxidizable substrates can reactivate mitochondrial oxidative phosphorylation, thereby allowing cellular ATP to recover to a level consistent with cell viability. This will not occur, however, if during the ischemic period the mitochondria are damaged to a point at which they are incapable of synthesizing ATP at a rate that is commensurate with cellular needs. Under these conditions, as well as during incomplete ischemia, the rate of glycolytic conversion of glucose to lactate accelerates in a futile and inefficient attempt to produce the necessary level of ATP. This may exacerbate the problem by creating a pathologically acidic intracellular environment due to the accumulation of lactic acid.[2]

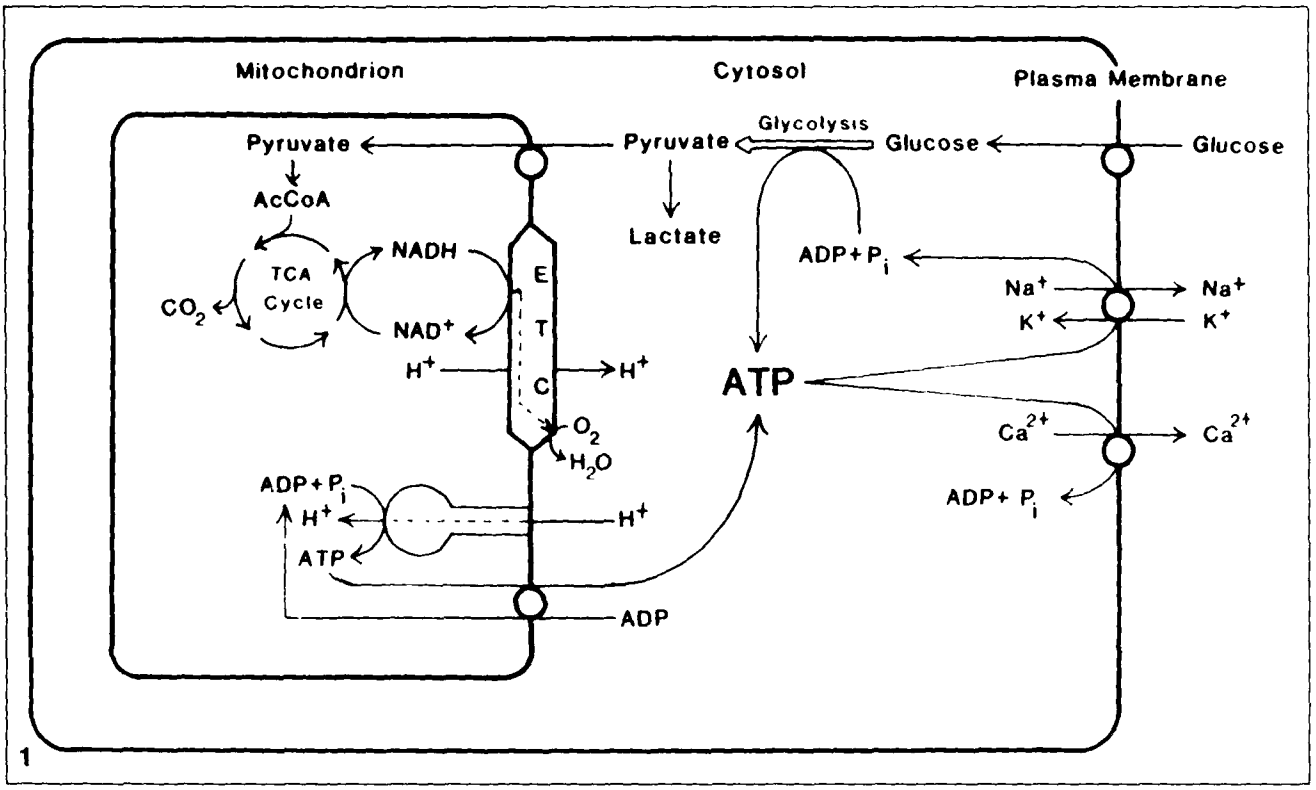


Fig. 1. *Cellular energy metabolism. The central nervous system obtains almost all of its energy from the oxidation of glucose. In the presence of oxygen, the pyruvate generated from glucose via glycolysis is further oxidized via the tricarboxylic acid (TCA) cycle located within the mitochondrion. The energy given off during this process is captured by the reduction of oxidized pyridine nucleotides, eg, nicotinamide adenine dinucleotide (NAD^+). These reduced high-energy molecules are oxidized by the electron transport chain (ETC), which is located at the mitochondrial inner membrane. The energy given off during the transport of electrons from NADH to O_2 is used to pump protons out of the mitochondrion. The resultant electrochemical gradient of protons drives the synthesis of ATP during the downhill reentry of protons into the mitochondrion via the membrane-bound ATP synthetase. ATP is then transported out of the mitochondrion into the cytosol, where it is used to drive such energy-requiring reactions as the active transport of Na^+ and Ca^{2+} out of the cell. In the absence of O_2, relatively little ATP is produced during the glycolytic breakdown of glucose to lactic acid.*

In addition to being the primary generator of ATP, respiring mitochondria are capable of actively accumulating large amounts of Ca^{2+}, thereby buffering the Ca^{2+} concentration of the surrounding milieux at 1 μM or less. This process is not the primary mechanism responsible for controlling the cytosolic Ca^{2+} concentration under normal conditions; however, it is believed to be an important back-up system when the level of intracellular Ca^{2+} becomes abnormally elevated.[3] Thus mitochondrial Ca^{2+} sequestration during postischemic reperfusion may represent an important line of defense against continued Ca^{2+}-dependent cellular damage, at least until ATP reaches a level that is sufficient to pump the excess Ca^{2+} out of the cell.

Mitochondrial Ca^{2+} uptake and oxidative phosphorylation both depend on the respiration-dependent electrochemical gradient of protons to fuel their activities. Therefore, when ischemia causes damage to the mitochondrial electron transport chain, the accumulation of Ca^{2+} is inhibited, as is the synthesis of ATP.[4] This, in turn, can prolong the time during which Ca^{2+}-activated degradative enzymes can act on cellular constituents and possibly potentiate the onset of irreversible cellular injury.

The possibility that intracellular Ca^{2+} can remain elevated during reperfusion suggests that cellular damage does not necessarily stop at the end of ischemia. In fact, considerable evidence indicates that reperfusion often does cause further damage to cellular activities,[5] including oxidative phosphorylation.[6] It is widely believed, however, that postischemic damage is primarily due to biochemical alterations inflicted by elevated levels of free radicals, such as superoxide (O_2^-) and hydroxyl radicals ($OH^\cdot$).[7] In the presence of certain catalysts (eg, "free" iron) free radicals react readily with membrane lipids, causing extensive alterations in the structure and function of cell membranes.[8] All cells possess enzymes (eg, superoxide dismutase, catalase, and glutathione peroxidase) that can detoxify free radicals and their metabolites. Postischemic detoxification may be limited, however, particularly if the activity of these enzymes is reduced during the

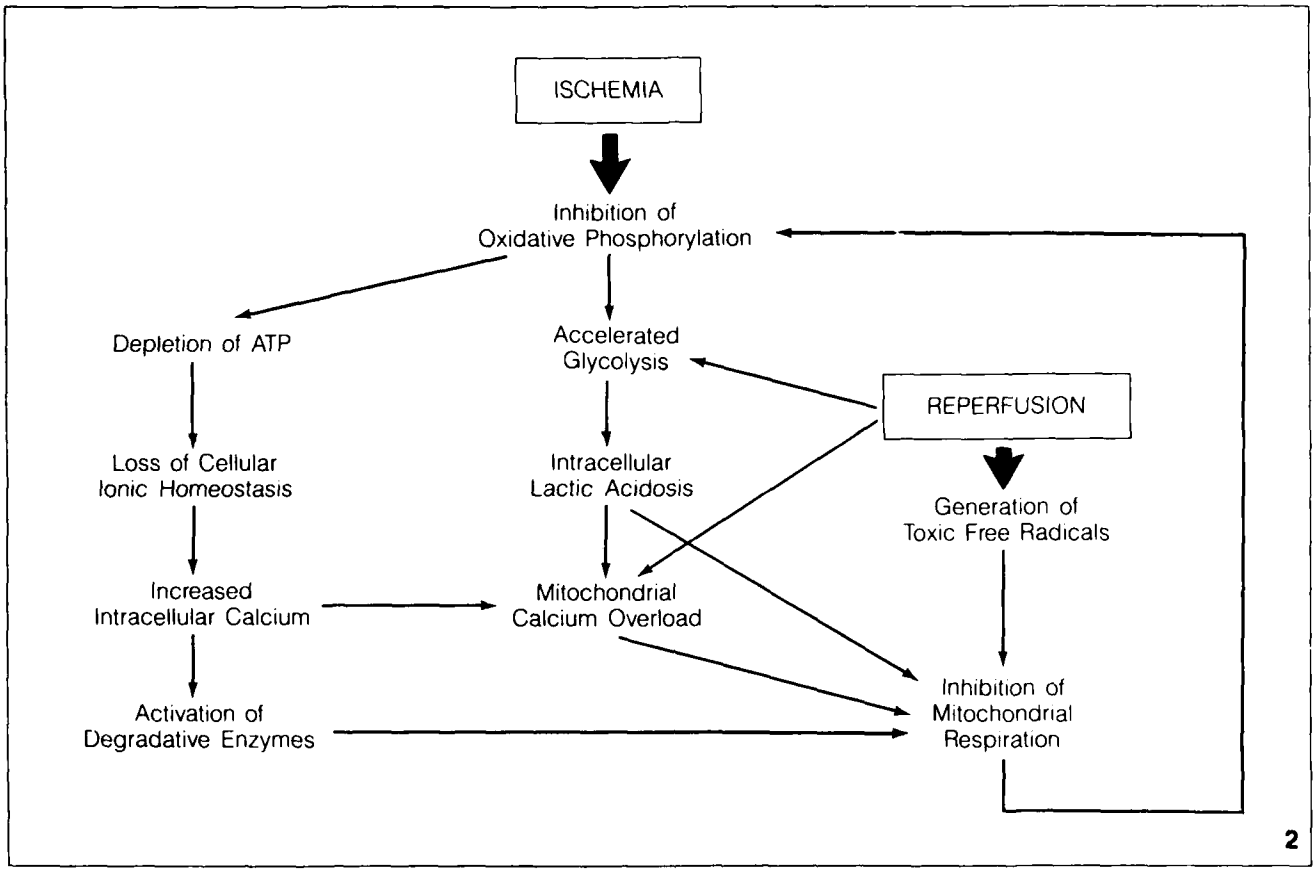


Fig. 2. *Mitochondrial damage during ischemia and reperfusion.*

period of ischemia. The self-sustaining nature of free radical reactions also can lead to the slow accumulation of abnormal molecules that may take many hours to be reflected as an alteration of tissue function.

Mitochondrial Damage During Ischemia and Reperfusion

Many studies have examined the alterations of mitochondrial activities that occur during ischemia. These experiments have been performed primarily with liver, heart, and kidney mitochondria and, to a lesser extent, with brain mitochondria.[4] Extrapolation of results obtained with one tissue to another is unwise because of the great variability in the metabolic activities of different types of cells. Therefore, this discussion will focus on the effects of ischemia and reperfusion on brain mitochondria.

The influence of ischemia on brain mitochondria has been assessed in animal models employing complete or incomplete ischemia with or without reperfusion. At different durations of ischemia or postischemic reperfusion, the animals are sacrificed and the mitochondria are isolated from the brain. Depending on the procedure, the isolated mitochondria can be primarily those present within synaptosomes, those that are "free" and not encapsulated by synaptosomal membranes, or a combination of both. The effects of ischemia on these different populations of brain mitochondria have not been rigorously compared. This should be done because there is evidence that there are significant differences in the normal metabolic activities of "free" compared to synaptosomal mitochondria.[9]

Comparisons between the activities of normal and ischemic brain mitochondria have been restricted primarily to rates of electron-transport-dependent oxygen consumption. There are two fundamental types of mitochondrial oxygen consumption. Phosphorylating (State 3) respiration is that observed in the presence of ADP + P_i. Resting (State 4) respiration is that obtained prior to the addition of ADP or after the phosphorylation of ADP to ATP is completed. Several studies have shown that within minutes after the onset of complete or incomplete cerebral ischemia, there is a substantial decline in the maximum rate of State 3 respiration by brain mitochondria.[6,10-13] Typically there is at least a 50% inhibition of ADP-stimulated respiration after 15 minutes of ischemia and 75% inhibition by 30 minutes of ischemia. This is due to a decline in the activity of the mitochondrial electron transport chain rather than an inactivation of the enzymes directly responsible for ATP synthesis and transport.[12] Surprisingly, State 4 respiration by brain mitochondria is unaffected by up to one hour of cerebral ischemia.[12,13] This finding contrasts with those made with other tissues, such as liver and kidney, in which ischemia induces an elevation in the rate of resting respiration (uncoupling) due to an increase in the nonspecific ion permeability of the mitochondrial inner-membrane.[4]

One very important observation is that mitochondria isolated from ischemic brains possess the ability to recover in vivo during reperfusion following a relatively long period of complete ischemia. After 30 minutes of reperfusion following 30 minutes of complete ischemia, there is a total recovery of the rate of State 3 respiration by rat brain mitochondria.[6,11,12] If reperfusion follows 30 minutes of incomplete ischemia, however, ADP-stimulated O_2 consumption either fails to recover to the control value[12] or actually falls to a level that is even lower than that obtained in the presence of ischemia alone.[6,11]

Unfortunately, very limited data are available concerning the long-term status of oxidative phosphorylation after ischemia and reperfusion. In one study using a rat model, mitochondrial impairment did appear to progress after 72 hours of postischemic reperfusion.[14] Clearly, more studies are needed to assess the temporal relationship between mitochondrial damage and delayed neurological injury.

During the early stages of postischemic reperfusion, mitochondrial Ca^{2+} accumulation may be just as important as the synthesis of ATP in establishing an intracellular environment that is adequate for neuronal survival. When reperfusion follows more than five minutes of complete ischemia (where ATP is completely depleted[15]), the respiration-dependent process of mitochondrial Ca^{2+} uptake is the only mechanism initially available for lowering the concentration of cytosolic Ca^{2+}. The rate and capacity of brain mitochondria for accumulating Ca^{2+} are significantly depressed after 15 or 30 minutes of ischemia;[13] however, the maximal capacity for Ca^{2+} sequestration does not decline as rapidly as oxidative phosphorylation does, and it appears to exceed what would be necessary for the preliminary buffering of cytosolic Ca^{2+} after as much as 30 minutes of ischemia (F Hamud and G Fiskum, unpublished results).

Mechanisms of Mitochondrial Damage

The primary factors believed to be involved in the damage of brain mitochondria during ischemia and reperfusion are intracellular lactic acidosis; Ca^{2+}-activated degradative enzyme activities; mitochondrial Ca^{2+} overload; and free-radical-induced membrane lipid peroxidation.

An acidic environment is known to inhibit mitochondrial respiration and Ca^{2+} accumulation. In vitro acidosis of pH 6.4 has been shown to inhibit ADP-stimulated brain mitochondrial respiration by 50% compared to the rate obtained at pH 7.2.[16] This effect is only partially reversed by neutralizing the pH after the mitochondria have been exposed to acidic pH values for only five minutes. A pH of 6.0 has also been shown to cause an inhibition of the maximal capacity for Ca^{2+} sequestration by normal or ischemic brain mitochondria.[13] These effects are consistent with the pattern of mitochondrial damage caused by ischemia, and they correlate with the relatively poor recovery of mitochondria from brains that are reperfused following incomplete versus complete 30-minute ischemia. However, recent results, obtained with mitochondria isolated from high and low lactate animals that were exposed to 30 minutes of reperfusion following 15 minutes of complete ischemia, suggest that lactic acidosis does not impair the ability of mitochondria to recover under these more moderate conditions.[17]

The possibility that much of ischemia-associated mitochondrial damage is due to the deleterious action of Ca^{2+}-dependent enzymes on mitochondrial components is quite attractive, particularly in light of what is already known concerning the involvement of Ca^{2+} in other forms of cellular injury.[1] There is little direct evidence, however, for Ca^{2+}-activated mitochondrial membrane damage in the ischemic brain. The most widely cited Ca^{2+}-dependent degradative enzyme is phospholipase A2. This enzyme catalyzes the hydrolysis of polyunsaturated fatty acyl groups (eg, arachidonate) from membrane phospholipids, thereby generating free fatty acids and lysophospholipids. The in vitro exposure of mitochondria to phospholipase A2 or its products can cause extensive mitochondrial alterations, including inhibition of oxidative phosphorylation and Ca^{2+} retention.[18] These agents generally cause an increase in State 4 respiration due to an increase in the leakiness of the mitochondrial membrane. Because this is not observed in isolated ischemic brain mitochondria, the direct involvement of phospholipase A2 in the damage to this organelle is questionable. Also, comparisons between the phospholipase activities of mitochondria from different tissues indicate that brain mitochondria possess a particularly low phospholipase A2 activity.[17]

There is still a good possibility that Ca^{2+}-activated enzymes could at least indirectly contribute to the damage observed in ischemic brain mitochondria, and this connection has been made in other types of ischemic tissues such as liver.[1] An answer to this question will require biochemical analyses of mitochondrial membrane lipids and proteins in model systems in which cerebral ischemia and reperfusion is carried out in the absence and presence of Ca^{2+} antagonists.

The abnormal accumulation of Ca^{2+} by reenergized mitochondria during reperfusion has often been cited as a potential cause of postischemic mitochondrial damage.[1] Excessive Ca^{2+} accumulation can cause either osmotic lysis and irreversible membrane disruption[18] or reversible inhibition of ADP-stimulated respiration.[21] The former event probably does not occur in brain mitochondria because of their extremely high capacity for energy-coupled Ca^{2+} sequestration;[19] however, brain mitochondria are particularly susceptible to inhibition of oxidative phosphorylation by loads of Ca^{2+} that could be reached during reperfusion.[21] This, in turn, could retard the rate of cellular reenergization, but it would not explain the low rates of mitochondrial respiration in vitro because isolated mitochondria normally do not retain the Ca^{2+} that is accumulated in vivo. Thus no differences have been observed in the content of Ca^{2+} located within mitochondria isolated from normal, ischemic, and reperfused rat brains.[17] Clarification of the role of post-ischemic mitochondrial Ca^{2+} accumulation in the respiratory activities of brain mitochondria will depend on determinations of mitochondrial Ca^{2+} levels in situ, such as those that can be accomplished with the aid of electron microprobe analyses.[22]

The potential for mitochondrial injury by oxygen free radicals during incomplete ischemia or reperfusion also is based primarily on in vitro studies. It is well established that O_2^- and OH^- can cause mitochondrial membrane lipid peroxidation which results in the inhibition of mitochondrial respiration.[23] Brain mitochondria have been shown to undergo significant altera-

tions of State 3 (but not State 4) respiration in the presence of an oxygen-free-radical-generating system consisting of hypoxanthine, xanthine oxidase, and Fe^{2+}.[8] Hypoxanthine can be generated during ischemia as a catabolic product of adenine nucleotides,[24] and evidence exists that "free" iron is liberated in the brain during reperfusion;[25] thus this model system may actually reflect one of the pathological events that occurs in vivo. The confirmation of this hypothesis will require detailed biochemical determinations of the type and extent of mitochondrial membrane lipid oxygenation that occurs during incomplete ischemia and, most importantly, during extended periods of reperfusion.

Summary and Conclusions

The likely sequence of events that relate to mitochondrial damage during cerebral ischemia and reperfusion is summarized (Figure 2). Ischemic anoxia immediately causes a profound inhibition or termination of oxidative phosphorylation. The associated lack of mitochondrial pyruvate production and drop in the ATP concentration stimulates the glycolytic production of lactic acid from glucose. This produces only a slight depression in the intracellular pH during complete ischemia; however, pathological pH values of 6.0 or less can be obtained during incomplete ischemia when lactate continues to accumulate.

Glucose and creatine phosphate are depleted within minutes after the onset of complete ischemia. At this juncture, ATP also is virtually absent due to its continual utilization by energy-requiring reactions. This causes a drop in the gradients of ions across cellular membranes. When the cytosolic Ca^{2+} concentration rises above approximately 1 μM, degradative enzymes (eg, phospholipases and proteases) initiate the destruction of mitochondria and other cellular constituents.

Reperfusion of ischemic tissue provides the glucose needed for glycolysis and the O_2 needed for mitochondrial respiration. Eventually the two processes will produce enough ATP to reenergize the cell and establish normal ionic homeostasis. If the mitochondrial electron transport chain is operating at an abnormally low rate, however, glycolysis and lactate production may be accelerated. This could be further potentiated by inhibition of respiration due to excessive mitochondrial Ca^{2+} accumulation. Reperfusion and incomplete ischemia also could lead to the generation of toxic oxygen free radicals which may also contribute to mitochondrial inhibition by lipid peroxidation. This last process is relatively slow, albeit self-perpetuating, and may explain the delayed tissue damage observed many hours or even days after the ischemic episode.

Intervention in the pathophysiology of ischemic mitochondrial damage can occur in several different ways. Infusion of ATP during reperfusion can elevate intracellular ATP,[26] thereby decreasing the rate of glycolysis and inhibiting intracellular lactic acidosis. It may also improve the recovery of mitochondria by promoting anabolic reactions, such as the reacylation of mitochondrial lysophospholipids. Accelerated ATP-dependent cellular Ca^{2+} efflux also would be expected to diminish the need for respiration-dependent uptake of Ca^{2+} by reenergized mitochondria. Whatever the mechanism of improvement may be, perfusion with ATP has been shown to amend significantly mitochondrial function following hepatic ischemia.[27]

The pathological effects of Ca^{2+} on mitochondrial function can potentially be dealt with by a variety of drugs. Ca^{2+} channel blockers decrease cellular Ca^{2+} influx[28] and lower the postischemic cerebral tissue content of Ca^{2+}.[29] There is also some evidence that they can act directly on the mitochondrial membrane[29,30] and inhibit Ca^{2+} uptake-induced mitochondrial damage.[31] Pretreatment of experimental animals with verapamil prior to 60 minutes of myocardial ischemia preserves the normal Ca^{2+} transport activities of heart mitochondria.[30] It remains to be seen whether postischemic administration of Ca^{2+} channel blockers improves the respiratory and Ca^{2+} transport capacities of isolated brain mitochondria. Other Ca^{2+} antagonists (eg, chlorpromazine) have been demonstrated to ameliorate the damage incurred by liver mitochondria during either anoxia in vitro[32] or ischemia in vivo.[33] These and other similar observations could provide a rationale for the beneficial effects of Ca^{2+} channel blockers during cerebral resuscitation, for recent evidence indicates that they do not act simply by preservation of cerebral perfusion.[34]

The involvement of oxygen free radicals in ischemic mitochondrial injury could be probed for, and possibly inhibited by, several different drugs. Mitochondrial lipid peroxidation in vitro can be inhibited by the quinone compound idebenone[34] and by both chlorpromazine and mepacrine.[32] Chelation of delocalized iron by desferrioxamine also can act effectively as a scavenger of superoxide radicals;[35] however, the effect of this drug on mitochondrial respiration and lipid peroxidation has not been reported. Thus it will be particularly interesting to determine what relationships exist between the effects of these agents on delayed ischemic neurological impairment and the structure and function of the mitochondrial membrane.

References

1. Faber JE: Membrane injury and calcium homeostasis in the pathogenesis of coagulative necrosis. *Lab Invest* 1982, 47:114-123.

2. Rehncrona S, Kagstrom E: Tissue lactic acidosis and ischemic brain damage. *Am J Emerg Med* 1983;1:168-174.

3. Fiskum G: Physiological aspects of mitochondrial calcium transport, in Sigel H (ed): *Metal Ions in Biological Systems, Vol 17: Calcium and Its Role in Biology.* Marcel Dekker, New York, 1983, pp 187-214.

4. Fiskum G: Involvement of mitochondria in ischemic cell injury and in regulation of intracellular calcium. *Am J Emerg Med* 1983;1:147-153.

5. Pulsinelli WA, Brierley JB, Plum F: Temporal profile of neuronal damage in a model of transient forebrain ischemia. *Ann Neurol* 1982;11:491-498.

6. Rehncrona S, Mela L, Siesjo BK: Recovery of brain mitochondrial function in the rat after complete and incomplete cerebral ischemia. *Stroke* 1979;10:437-446.

7. White BC, Aust SD, Arfors KE, et al: Brain injury by ischemic anoxia. Hypothesis extension — A tale of two ions? *Ann Emerg Med* 1984;13:862-867.

8. Hillered L, Ernster L: Respiratory activity of isolated rat brain mitochondria following *in vitro* exposure to oxygen radicals. *J Cereb Blood Flow Metab* 1983, 3:201-214.

9. Leong SF, Lai JCK, Lim L, et al: The activities of some energy metabolising enzymes in nonsynaptic (free) and synaptic mitochondria derived from selected brain regions. *J Neurochem* 184:42:1306-1312.

10. Ozawa K, Seta K, Araki H, et al: The effect of ischemia on mitochondrial metabolism. *J Biochem* 1967;61:s12-s14.

11. Mela L: Reversibility of mitochondrial metabolic response to circulatory shock and tissue ischemia. *Circ Shock [Suppl]* 1979;1:61-67.

12. Hillered L, Siesjo BK, Arfors KE: Mitochondrial response to transient forebrain ischemia and recirculation in the rat. *J Cereb Blood Flow Metab* 1984; 4:438-446.

13. Hamud F, Fiskum G: Loss of maximal respiratory and Ca^{2+} uptake capacities by rat brain mitochondria during cerebral ischemia, (abstract). *Biophys J* 1985;47:414a.

14. Kuwashima J, Fujitani B, Nakamura K, et al: Biochemical changes in unilateral brain injury in the rat: A possible role of free fatty acid accumulation. *Brain Res* 1976;110:547-557.

15. Ljunggren B, Schutz H, Siesjo BK: Changes in energy state and acid-base parameters of the rat brain during complete compression ischemia. *Brain Res* 1974; 73:277-289.

16. Hillered L, Ernster L, Siesjo BK: Influence of *in vitro* lactic acidosis and hypercapnia on respiratory activity of isolated rat brain mitochondria. *J Cereb Blood Flow Metab* 1984;4:430-437.

17. Hillered L, Smith ML, Siesjo BK: Lactic acidosis and recovery of mitochondrial function following forebrain ischemia in the rat. *J Cereb Blood Flow Metab* 1985; in press.

18. Beatrice MC, Palmer JW, Pfeiffer DR: The relationship between mitochondrial membrane permeability, membrane potential, and the retention of Ca^{2+} by mitochondria. *J Biol Chem* 1980;225: 8663-8671.

19. Fiskum G, Pfeiffer D, Broekemeir, KM, et al: Calcium buffering characteristics and phospholipase activities of rat brain mitochondria, (abstract). *Biophys J* 1985;47:413a.

20. Mittnacht S, Farber JL: Reversal of ischemic mitochondrial dysfunction. *J Biol Chem* 1981;256:3199-3206.

21. Hillered L, Muchiri PM, Nordenbrand, K, et al: Mn^{2+} prevents the Ca^{2+}-induced inhibition of ATP synthesis in brain mitochondria. *FEBS Letts* 1983; 154:247-250.

22. McGraw CF, Somlyo AV, Blaustein MP: Localization of calcium in presynaptic nerve terminals: An ultrastructural and electron microprobe analysis. *J Cell Biol* 1980;85:228-241.

23. Vladimirov YA, Olenev VI, Suslova TB, et al: Lipid peroxidation in mitochondrial membrane. *Adv Lipid Res* 1980; 17:173-249.

24. DeWall RA, Vasko KA, Stanley EL, et al: Responses of the ischemic myocardium to allopurinol. *Am Heart J* 1971; 82:362-370.

25. White BC, Krause GS, Aust SD, et al: Postischemic tissue injury by iron-mediated free radical lipid peroxidation. *Ann Emerg Med* 1985;14:804-809.

26. Sumpio BE, Chaudry IH, Clemens MG, et al: Accelerated functional recovery of isolated rat kidney with ATP-$MgCl_2$ after warm ischemia. *Am J Physiol* 1984;247:R1047-R1053.

27. Ohkawa M, Clemens MG, Chaudry IH: Studies on the mechanism of beneficial effects of ATP-$MgCl_2$ following hepatic ischemia. *Am J Physiol* 1983; 244:R695-R702.

28. Janis RA, Scriabine A: Sites of action of Ca^{2+} channel inhibitors. *Biochem Pharmacol* 1983;32:3499-3507.

29. DeGaravilla L, Babbs CF, Borowitz JL: Effect of diltiazem on brain calcium content following ischemia and reperfusion in a rat circulatory arrest model, (abstract). *Ann Emerg Med* 1984;13:384.

30. Wolkowicz PE, Michael LH, Lewis RM, et al: Sodium-calcium exchange in dog heart mitochondria: Effects of ischemia and verapamil. *Am J Physiol* 1983; 244:H644-H651.

31. Schwartz A, Grupp G, Millard RW, et al: Calcium channel blockers: Possible mechanisms of protective effects in the ischemic myocardium, in Weiss GB (ed): *New Perspectives on Calcium Antagonists*. American Physiology Society, 1981, pp 191-210.

32. Miyahara M, Okimasu E, Mikasa H, et al: Improvement of the anoxia-induced mitochondrial dysfunction by membrane modulation. *Arch Biochem Biophys* 1984;233:139-150.

33. Dean JM, Hoehner PJ, Rogers MC, et al: Effect of lidoflazine on cerebral blood flow following twelve minutes total cerebral ischemia. *Stroke* 1984;15:531-535.

34. Suno M, Nagaoka A: Inhibition of lipid peroxidation by a novel compound (CV-2619) in brain mitochondria and mode of action of the inhibition. *Biochem Biophys Res Commun* 1984;125: 1046-1052.

35. Sinaceur J, Robiere C, Nordmann J, et al: Desferrioxamine: A scavenger of superoxide radicals? *Biochem Pharm* 1984;33:1693-1694.

SPECIAL CONTRIBUTION
antioxidants; arachidonic acid;
eicosanoids; iron; lipid peroxidation; spinal cord trauma

Spinal Cord Injury and Protection

Subsequent to traumatic injury of the spinal cord, a series of pathophysiological events occurs in the injured tissue that leads to tissue destruction and paraplegia. These include hemorrhagic necrosis, ischemia, edema, inflammation, neuronophagia, loss of Ca^{2+} from the extracellular space, and loss of K^+ from the intracellular space. In addition, there is trauma-initiated lipid peroxidation and hydrolysis in cellular membranes. Both lipid peroxidation and hydrolysis can damage cells directly; hydrolysis also results in the formation of the biologically active prostaglandins and leukotrienes (eicosanoids). The time course of membrane lipid alterations seen in studies of antioxidant interventions suggests that posttraumatic ischemia, edema, inflammation, and ionic fluxes are the result of extensive membrane peroxidative reactions and lipolysis that produce vasoactive and chemotactic eicosanoids. A diverse group of compounds has been shown to be effective in ameliorating spinal cord injury in experimental animals. These include the synthetic glucocorticoid methylprednisolone sodium succinate (MPSS); the antioxidants vitamin E, selenium, and dimethyl sulfoxide (DMSO); the opiate antagonist naloxone; and thyrotropin-releasing hormone (TRH). With the exception of TRH, all of these agents have demonstrable antioxidant and/or anti-lipid-hydrolysis properties. Thus the effectiveness of these substances may lie in their ability to quench membrane peroxidative reactions or to inhibit the release of fatty acids from membrane phospholipids, or both. Whatever the mode of action, early administration appears to be a requirement for maximum effectiveness. [Anderson DK, Demediuk P, Saunders RD, Dugan LL, Means ED, Horrocks LA: Spinal cord injury and protection. Ann Emerg Med August 1985;14:816-821.]

Douglas K Anderson, PhD*
Paul Demediuk, PhD†
Royal D Saunders†
Laura L Dugan†
Eugene D Means, MD*
Lloyd A Horrocks, PhD†
Cincinnati, Ohio

From the Medical Research Service Cincinnati VA Medical Center and the Department of Neurology, University of Cincinnati College of Medicine Cincinnati,* and the Department of Physiological Chemistry, The Ohio State University, Columbus, Ohio.†

Presented at the 1985 UAEM IRIEM Research Symposium in Orlando, Florida, February 7-8, 1985

The work was supported by the Veterans Administration and by NIH Research Grants NS-08291 and NS-10165 and Training Grant NS-07091

Address for reprints: Douglas K Anderson PhD, Veterans Administration Medical Center (127), 3200 Vine Street, Cincinnati, Ohio 45220

INTRODUCTION

Spinal cord injury is physically, psychologically, socially, and economically devastating. It has been estimated that the annual incidence of spinal cord injury in the United States is 40 per million population, or about 10,000 new cases per year.[1] The most frequent victims are young men injured in automobile accidents. Currently there is no accepted, specific treatment for acute spinal cord injury, primarily because the pathophysiological events involved in posttraumatic destruction of spinal cord tissue are only beginning to be understood.

Trauma to the spinal cord triggers a progressive series of autodestructive events that lead to varying degrees of tissue necrosis and paralysis, depending on the severity of the injury. Pathological changes that occur in traumatized spinal cord tissue include petechial hemorrhage progressing to hemorrhagic necrosis; lipid peroxidation; lipid hydrolysis with subsequent prostaglandin and leukotriene (eicosanoid) formation; loss of Ca^{2+} from the extracellular space and loss of K^+ from the intracellular space; ischemia with consequent decline in tissue O_2 tension and energy metabolites and development of lactic acidosis; edema; and inflammation and neuronophagia by polymorphonuclear leukocytes (PMN).[2,3]

In spite of extensive investigation, the mechanisms responsible for the initiation and propagation of these pathophysiological and pathochemical events remain undetected. Recent evidence suggests, however, that the overall initiator of this autodestructive cascade of events is mechanical deformation of any type (ie, impact or compression), and that the primary sites of

TABLE 1. *Cholesterol and 25-hydroxycholesterol levels in cat spinal cord following compression injury*

	Control‡	1 min‡	5 + 10‡	5 + 15‡	5 + 30‡
Cholesterol*	6.9 ± 0.1	6.1 ± 0.2		6.0 ± 0.1	5.9 ± 0.2
25-OH cholesterol†	8.5 ± 0.4		9.5 ± 2.0		13.3 ± 3.1

*Values are means of four cats ± SEM. Units are μmol cholesterol/μmol sphingomyelin

†Values are means of three cats ± SEM. Units are mg 25-OH cholesterol/μmol sphingomyelin

‡The times are control (laminectomy + 90 min stabilization), 1 min compression (170 g), 5 + 10, 5 + 15, 5 + 30 (5 min compression plus 10, 15, or 30 min recovery, respectively).

injury are the cellular and subcellular membranes of neurons, glia, and vascular endothelial cells.[3] Lipid peroxidation and activation of membrane lipases, with release of fatty acids leading to production of eicosanoids, are the earliest mechanically stimulated biochemical events described thus far.[3]

This article reviews the pathophysiology of acute spinal cord injury in relation to, and with special emphasis on, posttraumatic membrane lipid changes. Therapeutic agents shown to be effective in restoring neurological function following spinal cord injury in experimental animals are reviewed, as are their proposed modes of action. Our concept of the sequence of events leading to posttraumatic autodestruction of spinal cord tissue is described.

PATHOPHYSIOLOGY OF SPINAL CORD INJURY

Until thirty years ago, physicians and investigators believed trauma to the spinal cord caused disruption of the long fiber tracts, resulting in immediate and irreversible damage to spinal cord tissue. In the mid 1950s, however, Freeman and Wright[4] suggested that the actual determinants of posttraumatic neurological deficit are pathological events that occur in the tissue after the mechanical trauma; prominent among these posttraumatic pathophysiological processes is a substantial decline in blood flow in the injured tissue. Subsequent studies have supported an ischemic etiology for postinjury tissue destruction,[5-9] although other investigators have questioned whether ischemia is the initiating or principal cause of posttraumatic tissue necrosis.[10-13]

It is difficult to assess the laboratory evidence for the contribution of posttraumatic ischemia to the destruction of spinal cord tissue, because investigators have used different animal species, injury models, and methodologies for measuring blood flow. Despite these difficulties, it appears that ischemia, although probably secondary to more basic cellular response to trauma, figures prominently in the death of spinal cord tissue following injury.

The histopathology of experimental spinal cord injury provides some important clues to the pathogenesis of spinal cord autodestruction. Histologically the cardinal feature of spinal cord injury is progressive hemorrhagic necrosis of gray and white matter in the first 24 hours following trauma.[2] This pattern and the prominent extravasation of blood into the spinal cord within minutes of injury led Demopoulos and his coworkers to propose that free-radical-induced lipid peroxidation (catalyzed by some component of blood, such as the transition metals iron or copper, and/or hemoglobin degradation products, such as hematin) may be involved in microcirculatory injury and autodestruction of spinal cord tissue.[14-16]

Free-Radical-Induced Lipid Peroxidation

Free radicals are molecules that have an unpaired electron and, consequently, are generally reactive chemical species. Free-radical-mediated tissue injury is the result of uncontrolled, abnormal reactions of these species with various cell components. Although a variety of free radicals exist, the non-lipid free radicals of importance in spinal cord injury appear to be those derived from the univalent reduction of oxygen — ie, the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH\cdot$). Polyunsaturated fatty acids (PUFAs), which are found largely in membranes, are very susceptible to radical attack. Lipid peroxidation is the oxidative degradation of polyunsaturated lipid. These reactions involve the direct reaction of oxygen-derived radicals with lipids to form lipid free radical intermediates and fatty acid hydroperoxides.[17] Lipid peroxidation can be a geometrically progressing chain reaction of radical reactions if the proper conditions exist (eg, if catalysts such as iron, which accelerates the reaction rates, are present).

Demopoulos and his coworkers have supported their free radical hypothesis of spinal cord damage with studies of free radical or peroxidation chemistry in traumatized spinal cord tissue from one hour to six weeks after injury. Utilizing a 400-g/cm contusion of the cat spinal cord, they found increases in tissue levels of malondialdehyde (a byproduct of peroxidized PUFAs),[16] and in specific cholesterol free radical oxidation products.[15] Tissue content of the antioxidant ascorbic acid was decreased, as were the PUFAs arachidonate and docosahexanoate, and "extractable" cholesterol.[14,15]

Recent evidence from our laboratory also suggests that peroxidative reactions occur in traumatized cat spinal cord shortly after injury. Thirty minutes after termination of five minutes of compression trauma, tissue levels of the endogenous antioxidant alpha-tocopherol (vitamin E) were essentially zero. Tissue cholesterol levels fell 11% after one minute of compression, and were 15% below control values 30 minutes after termination of five minutes of compression (Table 1). Also at 30 minutes postcompression there was a 61% increase in the tissue levels of 25-hydroxycholesterol, an auto-oxidation product of cholesterol (Table 1).

In addition, we have shown that levels of the free fatty acid (FFA) arach-

TABLE 2. *Arachidonic acid and eicosanoid levels in cat spinal cord following compression injury**

	Control	1 min†	5 min†	5 + 5†	5 + 15†	5 + 30†
Arachidonate‡	0.13 ± 0.06	0.39 ± 0.09	2.65 ± 0.39	2.52 ± 0.45	1.52 ± 0.45	0.34 ± 0.18
PGE_2§‖	0.76 ± 0.61	0.84 ± 0.97	4.77 ± 2.94	21.51 ± 7.26	20.69 ± 7.43	20.23 ± 7.31
$PGF_{2\alpha}$§‖	1.04 ± 0.92	2.30 ± 0.63	2.72 ± 1.45	10.66 ± 5.11	13.45 ± 2.91	25.09 ± 6.01
Prostacyclin§	0.46 ± 0.42	0.78 ± 0.42	2.42 ± 2.08	2.62 ± 1.58	1.87 ± 1.09	2.22 ± 1.34
Thromboxane§	0.92 ± 0.79	1.19 ± 0.79	1.45 ± 0.88	9.14 ± 2.10	9.39 ± 3.12	12.69 ± 3.35
SRS§‖	ND	ND	ND	ND	0.925 ± 0.111	0.571 ± 0.314

*The values are the means of four samples ± SD

†The times are control (laminectomy + 90 min stabilization), 1 min and 5 min of compression (170 g), 5 + 5, 5 + 15, 5 + 30 (5 min compression plus 5, 15, or 30 min recovery, respectively)

‡Results expressed as nmol μmol total lipid phosphorus

§Results expressed as pmol μmol sphingomyelin

‖Abbreviations are PGE_2 (prostaglandin E_2), $PGF_{2\alpha}$ (prostaglandin $F_{2\alpha}$), SRS (slow reactive substances, primarily leukotrienes C_4, D_4, and E_4)

ND not detectable

idonate and the products of arachidonate oxidation (prostaglandin E_2 [PGE_2], $F_{2\alpha}$ [$PGF_{2\alpha}$], and thromboxane [TxB_2]) were elevated many-fold in cat spinal cord immediately following compression trauma. Free radicals are generated during the oxidative catabolism of arachidonate that produces the prostaglandin endoperoxides,[18] thereby adding to the free radical load of the tissue.

We have demonstrated acute posttraumatic inflammation and phagocytosis of neuronal perikarya by PMNs in spinal cord gray matter.[19] Production of free radicals by phagocytic PMNs would also add to the level of these species in traumatized tissue.

The findings described serve to demonstrate that peroxidative processes are operative in spinal cord tissue after trauma; however, the actual role of these peroxidative mechanisms in contributing to posttraumatic autodestruction of spinal cord tissue must be inferred. Perhaps lipid peroxidation is an epiphenomenon or merely a scavenging mechanism of already dead tissue. On the other hand, lipid peroxidation may actually contribute to posttraumatic tissue necrosis and paralysis by participating in the destruction of viable cells and axons. The early onset of peroxidative reactions in traumatized tissue (ie, within one to five minutes postinjury) is consistent with the hypothesis that peroxidation is occurring in viable tissue.

The argument that lipid peroxidation actually damages tissue is strengthened when agents known to extinguish free radical and peroxidative reactions can be shown to prevent or reduce posttraumatic tissue loss and paraplegia. We have demonstrated that one agent with antioxidant properties, methylprednisolone sodium succinate (MPSS), is effective in reducing posttraumatic neurologic deficit and tissue loss in experimental animals.[20] Cats were subjected to compression trauma of the spinal cord (170 g/5 min). One hour after injury, the cats were given MPSS intravenously, 15 mg/kg/day for two days in three divided doses per day; followed by MPSS intramuscularly 15 mg/kg for one day, 7.5 mg/kg/day for three days, and 3.75 mg/kg/day for three days. The total treatment period was nine days. Steroid-treated cats showed earlier and more complete recovery of neurologic function ($P < .001$) and greater tissue preservation ($P < .005$) than did injured, untreated controls.[20] The finding that the glucocorticoid MPSS is a powerful antioxidant in large doses[21] suggests that it may exert its protective effect on damaged spinal cord tissue (in part) by quenching free-radical-induced peroxidative reactions. Glucocorticoids possess several properties in addition to their antioxidant capabilities, however, all of which could contribute to the protection of spinal cord tissue following trauma. MPSS is a potent antioxidant, but the extent to which this glucocorticoid reduces posttraumatic tissue damage by antioxidant mechanisms remains unclear because of its other actions.

We treated another group of cats orally with 1,000 IU alpha-tocopherol and 50 μg selenium daily for five days prior to spinal cord compression trauma. Preliminary findings reveal that three of five treated cats showed better neurologic recovery and less tissue necrosis than untreated controls (unpublished study). The other two treated cats had a poor to moderate recovery. Hall et al[22] have recently demonstrated that pretreatment of cats with the same regimen of alpha-tocopherol and selenium prevented posttraumatic ischemia completely in white matter for the first four hours after injury.

Unlike MPSS, alpha-tocopherol and selenium appear to function purely as antioxidants or radical scavengers. Alpha-tocopherol intercalates into cell membranes and terminates the chain reaction of lipid peroxidation by reacting with lipid-peroxy free radicals to form tocopherol quinones and dimers.[23] It also acts as a hydrogen donor or reducing agent for lipid peroxides.[24] The selenium-containing enzyme glutathione peroxidase helps remove initiators of peroxidation by enzymatically reducing intracellular H_2O_2 to H_2O, and by reducing fatty acid hydroperoxides.[25] These studies

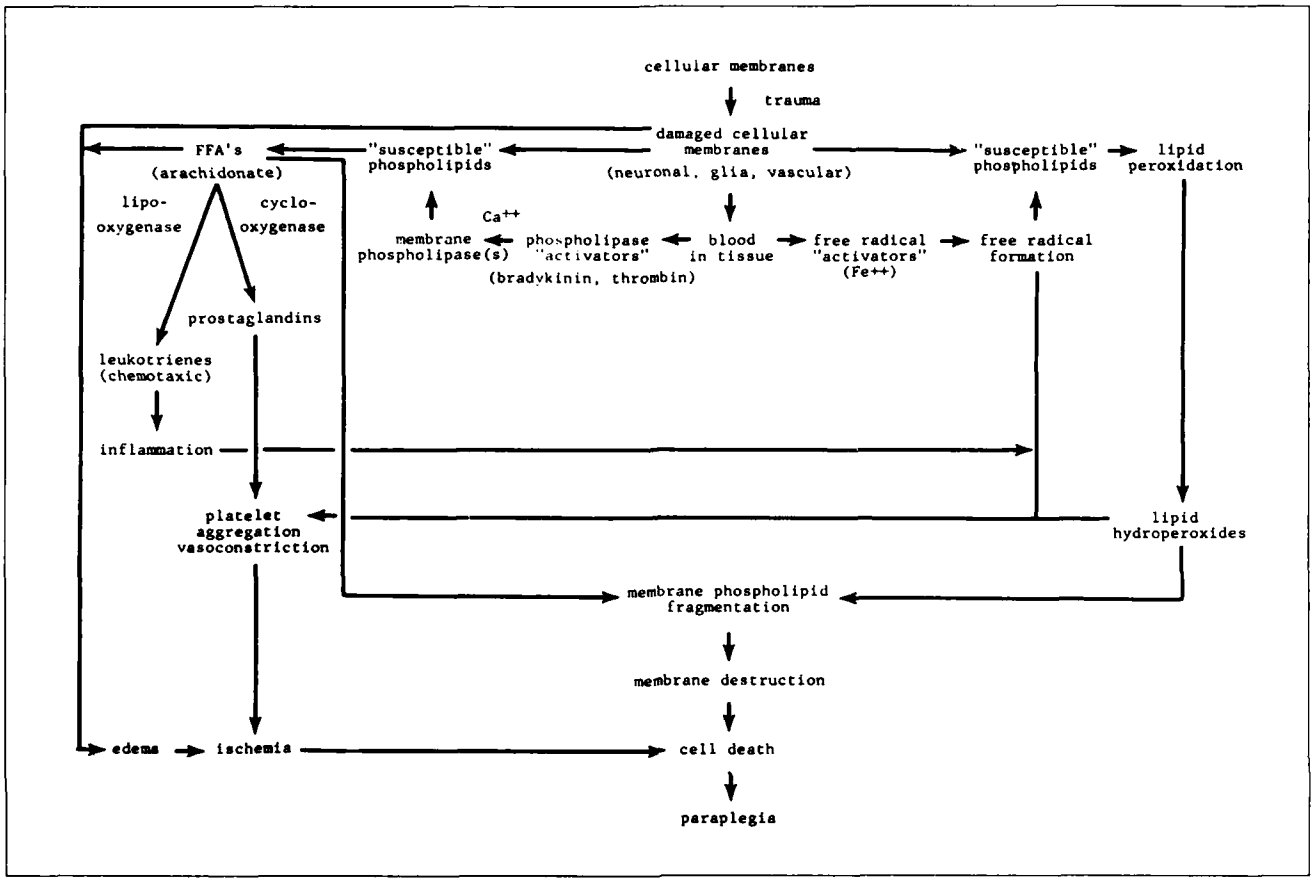


Fig. *Diagram of proposed mechanisms damaging cellular membranes subsequent to trauma that leads to secondary pathophysiological events (ie, edema, ischemia, and inflammation), tissue necrosis, and paralysis.*

provide preliminary evidence that lipid peroxidation is involved in posttraumatic destruction of viable spinal cord tissue.

Lipid Hydrolysis

Another prominent histological feature of spinal cord injury is the phagocytosis of neuronal perikarya by PMNs.[19] Four hours after compression trauma to the spinal cords of cats, PMNs were apparent in the walls of, and adjacent to, veins and venules, but great numbers of PMNs were not observed in tissue until eight to 24 hours after injury. Acute inflammation was especially prominent in areas of hemorrhage, and in these areas PMNs frequently surrounded and phagocytized neuronal somata. This phagocytosis of neurons indicated that chemotactic factors were liberated from neurons following spinal cord trauma. Potential chemotactic factors include oxygenated fatty acids generated by free-radical reactions, or leukotrienes generated from free arachidonic acid by lipoxygenase.

The finding of an acute inflammatory reaction in traumatized spinal cord tissue suggests the possibility of a trauma-induced activation of membrane lipases. These lipases would hydrolyze membrane phospholipids, thereby liberating arachidonic acid (and other fatty acids) to serve as the substrate for cyclo-oxygenase and lipoxygenase. We have shown that immediately after compression trauma to the spinal cords of cats, there is substantial lipid hydrolysis, demonstrated by increased levels of FFAs and prostaglandins in the traumatized tissue. Of the individual FFAs assayed, arachidonic acid had the largest relative increase (20-fold after five minutes of compression) (Table 2).

Tissue prostaglandin levels were unaltered during five minutes of compression injury (Table 2), however, within five minutes postcompression, PGE_2 and $PGF_{2\alpha}$ were elevated 24- and 10-fold, respectively. After 30 minutes, the tissue $PGF_{2\alpha}$ concentration had risen 24-fold above preinjury levels. Thromboxane levels also were increased 10-fold within five minutes after release from five minutes of compression (Table 2). There were no significant changes in tissue prostacyclin levels during the 30-minute postcompression period.

We found recently that slow reactive substances (SRS; ie, leukotrienes C_4, D_4, and E_4) were substantially elevated in traumatized spinal cord tissue. These lipoxygenase products increased from undetectable levels in uninjured tissue to 0.9 pmol by 15 minutes after termination of five minutes of compression (Table 2). This finding indicates that both the cyclo-oxygenase and lipoxygenase pathways are operative in traumatized spinal cord tissue and that products from either may contribute to the initiation or propagation (or both) of posttraumatic spinal cord ischemia, edema, and inflammation.

TISSUE AUTODESTRUCTION: A HYPOTHESIS

Our hypothesis of the mechanism leading to the autodestruction of spinal cord tissue begins with the traumatic disarrangement of neuronal, glial, and endothelial cell membranes (Figure). This mechanical perturbation of cell membranes could dislocate or decompartmentalize endogenous cellular iron and/or Ca^{2+} from inactive stores and activate membrane lipases. Subsequent to the initial traumatic event, Fe^{2+}, hematin, and other free-radical-generating hemoglobin degradation products extravasate into spinal cord tissue, thereby accelerating the free-radical-induced lipid peroxidation of membrane PUFAs and cholesterol. Additionally, clotting factors (such as thrombin) and products of coagulation (bradykinin) extravasate into spinal cord parenchyma with blood (along with the Ca^{2+} mobilization in cells and the production of free radicals), and support the activation of membrane lipases and the liberation of fatty acids, including arachidonate. This stimulation of membrane lipases, together with the loss of membrane cholesterol and lipids by auto-oxidation, can damage cells by altering membrane structure and permeability. These membrane alterations could account for the rapid decrease in extracellular Ca^{2+} and intracellular K^+ that is seen after injury.[24] Edema formation caused by injury of the spinal cord microvasculature could be exacerbated by the liberated PUFAs (particularly arachidonate) and by certain of the leukotrienes.

Arachidonic acid is metabolized by lipoxygenase to produce leukotrienes and by cyclo-oxygenase to produce prostaglandins. Certain of the leukotrienes may be the chemotaxins responsible for the migration to, and phagocytosis of, neurons by PMNs. In addition, both leukotrienes and prostaglandins are vasoactive.[18,25] Thromboxane is a potent vasoconstrictor that promotes platelet aggregation, whereas prostacyclin is a vasodilator and antiaggregant.[18] Thus the posttraumatic decrease in spinal cord blood flow may, in part, be due to platelet thrombi and vasoconstriction that are consequent to the increase in thromboxane synthesis relative to that of prostacyclin.

The lack of prostacyclin synthesis may derive from the inactivation of endothelial prostacyclin synthetase by lipid hydroperoxides.[26] The nidus for the formation of platelet thrombi could be crater-like lesions in the endothelial membrane caused by free radical reactions.[27] Posttraumatic vasoconstriction of the spinal cord vasculature also could be enhanced by elevated levels of $PGF_{2\alpha}$ and SRS.

Therefore we suggest that the primary site of early cellular damage following spinal cord injury may be the plasma membrane. Resulting from, and contributing to, this membrane injury is a potential cascade of interrelated pathochemical events that could play a prominent role in the posttraumatic autodestruction of spinal cord tissue.

EXPERIMENTAL THERAPIES

As discussed above, the synthetic glucocorticoid MPSS, or the antioxidants alpha-tocopherol and selenium, enhanced neurologic recovery in cats subjected to spinal cord compression injury. In addition, there are other, apparently unrelated, substances that have been effective in reducing the posttraumatic neurological deficit of experimental animals. De la Torre reported that the solvent dimethyl sulfoxide (DMSO) accelerated motor recovery in dogs subjected to impact trauma.[28] The opiate antagonist naloxone also has been shown to be effective in improving neurological recovery following impact trauma in cats.[29-32] In addition, naloxone significantly improved posttraumatic blood flow in both gray[30] and white matter,[30,33] and preserved somatosensory-evoked potentials following trauma.[32,33] Recently Faden and his coworkers demonstrated that treatment with the neuropeptide thyrotropin-releasing hormone (TRH) enhanced neurologic recovery from spinal cord injury in cats.[34,35] Their data indicated that TRH was more effective than either naloxone or dexamethasone in promoting posttraumatic neurologic recovery.[35]

The mechanisms underlying the effectiveness of this diverse group of agents are unknown. There may exist a commonality among these compounds that is not immediately apparent. As indicated earlier, MPSS and alpha-tocopherol and selenium are potent antioxidants. Naloxone has been shown to inhibit non-catalyzed peroxidation in liposomes, which suggests that this opiate-antagonist can act as an antioxidant in circumstances involving metal-catalyzed lipid peroxidation.[36] DMSO is also purported to be a free radical scavenger.[37,38] The data permit speculation that these agents may be acting, at least in part, through a common mechanism to retard the effects of spinal cord injury, by quenching the peroxidative reactions associated with this injury. It has been demonstrated that binding of TRH results in great changes in the fluidity of the lipid region of pituitary membrane,[39] but it remains to be determined whether TRH has any antioxidant potential.

Also to be determined is the effectiveness of these agents (and perhaps others) in ameliorating the effects of spinal cord injury in human beings. It may be that individual pharmacologic agents are not maximally effective; perhaps combinations of these (or other) agents will be necessary. Our data demonstrate that membrane lipid changes begin within one to five minutes of injury. This suggests that, for maximum effectiveness, any therapy should be started as soon as possible after injury, ie, at the accident site. As the understanding of the basic pathophysiology of spinal cord injury increases, and as the need for early and intensive pharmacologic therapy is appreciated, substantial improvement in the neurologic recovery of spinal cord injury victims should be expected.

REFERENCES

1. Bracken MB, Freeman DH, Hellenbrand K: Incidence of acute traumatic hospitalized spinal cord injury in the United States, 1970-1977. *Am J Epidemiol* 1981;113:615-622.

2. Means ED, Anderson DK: The pathophysiology of acute spinal cord injury. In Davidoff RA (ed): *Handbook of the Spinal Cord*. Marcel Dekker Publishers, vol 5, in press 1985.

3. Demediuk P, Saunders RD, Anderson DK, et al: Membrane lipid changes in laminectomized and traumatized cat spinal cord. *Proc Nat Acad Sci US/Biol Sci*, in press, 1985.

4. Freeman LW, Wright LW: Experimental observations of concussion and contusion of the spinal cord. *Ann Surg* 1953; 137:433-443.

5. Griffiths IR: Spinal cord blood flow after acute experimental cord injury in dogs. *J Neurol Sci* 1976;27:247-259.

6. Rivlin AS, Tator CH: Regional spinal cord blood flow in rats after severe cord trauma. *J Neurosurg* 1978;49:844-853.

7. Sandler AN, Tator CH: Effect of acute spinal cord compression injury on regional spinal cord blood flow in primates. *J Neurosurg* 1976;45:660-676.

8. Senter JH, Venes JL: Loss of autoregulation and post-traumatic ischemia following experimental spinal cord trauma. *J Neurosurg* 1979;50:198-206.

9. Young W, Flamm ES: Effect of high-dose corticosteroid therapy on blood flow, evoked potentials and extracellular calcium in experimental spinal injury. *J Neurosurg* 1982;57:667-673.

10. Bingham WH, Goldman H, Friedman SE, et al: Blood flow in normal and injured monkey spinal cord. *J Neurosurg* 1975; 43:162-171.

11. Kobrine AI, Doyle TF: Role of histamine in posttraumatic spinal cord hyperemia and the luxury perfusion syndrome. *J Neurosurg* 1976;44:16-20.

12. Kobrine AI, Doyle TR, Martins AM: Local spinal cord blood flow in experimental traumatic myelopathy. *J Neurosurg* 1975;42:144-149.

13. Griffiths IR, Trench JG, Crawford RA: Spinal cord blood flow and conduction during experimental cord compression in normotensive and hypotensive dogs. *J Neurosurg* 1979;50:353-360.

14. Demopoulos HB, Flamm ES, Pietronigro DD, et al: The free radical pathology and the microcirculation in the major central nervous system disorders. *Acta Physiol Scand [Suppl]* 1980;492: 91-119.

15. Demopoulos HB, Flamm ES, Seligman ML, et al: Further studies on free radical pathology in the major central nervous system disorders: Effect of very high doses of methylprednisolone on the functional outcome, morphology, and chemistry of experimental spinal cord impact injury. *Can J Physiol Pharmacol* 1982; 60:1415-1424.

16. Milvy P, Kakari S, Cambell JB, et al: Paramagnetic species and radical products in cat spinal cord. *Ann NY Acad Sci* 1973;222:1102-1111.

17. Halliwell B, Gutteridge JMC: Oxygen toxicity, oxygen radicals, transition metals and disease. *Biochem J* 1984;219:1-14.

18. Siesjo BK: Cerebral circulation and metabolism. *J Neurosurg* 1984;60:883-908.

19. Means ED, Anderson DK: Neuronophagia by leucocytes in experimental spinal cord injury. *J Neuropathol Expl Neurol* 1983;42:707-719.

20. Means ED, Anderson DK, Waters TR, et al: Effect of methylprednisolone in compression trauma to the feline spinal cord. *J Neurosurg* 1981;55:200-208.

21. Anderson DK, Means ED: Iron-induced lipid peroxidation in spinal cord. Protection with mannitol and methylprednisolone. *Journal of Free Radicals in Biology and Medicine*, in press, 1985.

22. Hall ED, Wolf DL: Pathophysiological mechanisms in posttraumatic spinal cord ischemia. III. Involvement of microvascular lipid peroxidation. Submitted to *J Cereb Blood Flow Metab*, 1984.

23. Anderson DK, Means ED: Lipid peroxidation in spinal cord: $FeCl_3$ induction and protection with antioxidants. *Neurochem Pathol* 1983;1:249-264.

24. Stokes BT, Garwood M: Microelectrode assay of electrolytes in spinal cord injury, in Winn R (ed): *Recent Progress in Neural Trauma*. New York, Raven Press, in press, 1985.

25. Moskowitz MA, Kiwak KJ, Hekimian K, et al: Synthesis of compounds with properties of leukotrienes C_4 and D_4 in gerbil brains after ischemia and reperfusion. *Science* 1984;224:868-888.

26. Warso MA, Lands WEM: Pathophysiologic moduation of arachidonate metabolism. *Clin Physiol Biochem* 1984;2:70-77.

27. Povlishock JT, Kontos HA: The pathophysiology of pial and intraparenchymal vascular dysfunction, in Grossman RG, Guildenberg PL (eds): *Head Injury: Basic and Clinical Aspects*. New York, Raven Press, 1982, pp 15-29.

28. de la Torre JC, Kawanaga HM, Rowed DW, et al: Dimethyl sulfoxide in central nervous system trauma. *Ann NY Acad Sci* 1975;243:362-389.

29. Faden AI, Jacobs TP, Holaday JW: Opiate antagonist improve neurologic recovery after spinal injury. *Science* 1981;211:493-494.

30. Faden AI, Jacobs TP, Mougey E, et al: Endorphins in experimental spinal injury: Therapeutic effect of naloxone. *Ann Neurol* 1981;10:326-332.

31. Faden AI, Jacobs TP, Holaday JW: Comparison of early and late naloxone treatment in experimental spinal injury. *Neurology* 1982;32:677-681.

32. Flamm ES, Young W, Demopoulos HB, et al: Experimental spinal cord injury: Treatment with naloxone. *Neurosurgery* 1982;10:227-231.

33. Young W, Flamm ES, Demopoulos HB, et al: Effect of naloxone on posttraumatic ischemia in experimental spinal contusion. *J Neurosurg* 1981;55: 209-219.

34. Faden AI, Jacobs TP, Holaday JW: Thyrotropin-releasing hormone improves neurologic recovery after spinal trauma in cats. *N Engl J Med* 1981;305:1063-1067.

35. Faden AI, Jacobs TP, Smith MT, et al: Comparison of thyrotropin-releasing hormone (TRH), naloxone, and dexamethasone treatments in experimental spinal injury. *Neurology* 1983;33:673-678.

36. Koreh K, Seligman ML, Flamm ES, et al: Lipid antioxidant properties of naloxone *in vitro*. *Biochem Biophys Res Comm* 1981;102:1317-1322.

37. Panganamala RV, Sharma HM, Heikkila RE: Role of hydroxyl radical scavengers, dimethyl sulfoxide, alcohols and methional in the inhibition of prostaglandin synthesis. *Prostaglandins* 1976;11: 599-604.

38. Ward PA, Till GO, Kunkel R, et al: Evidence for role of hydroxyl radical in complement and neutrophil-dependent tissue injury. *J Clin Invest* 1983;72: 789-801.

39. Smith ICP, Schreier-Muccillo S, Marsh D: Spin labeling, in Pryor WA (ed): *Free Radicals in Biology*. New York, Academic Press, 1976, Vol I, pp 149-197.

Motor Vehicle Safety

[This document was developed by the American College of Emergency Physicians Public Relations Committee, and was approved by the Board of Directors on April 25, 1985. American College of Emergency Physicians: Motor vehicle safety, position paper. Ann Emerg Med August 1985;14:822-823.]

American College of
Emergency Physicians
Dallas, Texas

Address for reprints: American College of
Emergency Physicians, PO Box 619911,
Dallas, Texas 75261-9911

Emergency physicians are usually the first medical professionals to treat victims of motor vehicle accidents. Frequently they also minister to the families of victims who have died or suffered permanent injury.

In response to this human loss and tragedy witnessed by emergency physicians every day, the American College of Emergency Physicians (ACEP) has adopted the position that traffic safety measures must be mandated and enforced when possible. Safety laws are not an infringement on individual rights; they are a means to reduce the morbidity and mortality rates stemming from motor vehicle accidents, and to permit reallocation of society's resources to more beneficial programs.

The following laws or regulations should be enacted and enforced:

- Require motorcyclists and riders on all other similar vehicles, including but not limited to mopeds, bicycles, snowmobiles, and all-terrain vehicles, to wear helmets.
- Require motor vehicle drivers and passengers to wear seat belts.
- Require passive restraints in all new car models manufactured after September 1, 1989.
- Require that all children under age 4 or under 40 pounds be restrained in approved child restraint seats whenever riding in a motor vehicle.
- Require for drunk drivers a combination of mandatory rehabilitation programs and mandatory legal sanctions, such as suspension of the driver's license or a defined jail sentence.
- Establish a national legal drinking age of 21.
- Support "dram shop" laws that establish liability against any person who serves alcoholic beverages to an individual who is visibly intoxicated.
- Prohibit consumption of alcoholic beverages in motor vehicles.
- Prohibit possession of open alcoholic beverage containers in the passenger compartments of motor vehicles.
- Create a dedicated funding source within states and municipalities from DUI offender fines and fees to increase efforts in enforcement, prosecution, adjudication, education, and treatment of offenders.
- Establish an "implied consent" statute that provides that all licensed drivers have given their consent to blood, breath, or urine tests that will determine alcohol or drug concentrations.
- Permit police officers to use preliminary breath tests, and permit these tests to be admitted as evidence in DUI trials.
- Require mandatory testing of alcohol and drug levels of all fatally injured drivers and all drivers who are involved in a fatal or serious personal injury

crash in which there is probable cause to suspect substance abuse.

ACEP is strongly committed not only to legislation on these issues, but also to the following:

- Public education and awareness programs.
- Education and awareness programs for physicians and other health care professionals.
- Research to determine the causes of automobile accident morbidity and mortality, to identify measures to reduce this morbidity and mortality, and to monitor the effectiveness of public education programs and the impact of legislation.

ACEP encourages its members, as physicians and citizens, to take the lead in motor vehicle safety activities at the local, state, and national levels.

Just what the doctor ordered. A simple slit lamp for emergency eye care.

You may only use it once a day. Or maybe once a week. But when you need it, chances are you'll need it badly.

That's why Marco's Primary Care slit lamp is such a vital instrument for hospital emergency departments and industrial dispensaries. When time is critical in primary eye examination or foreign object removal, Marco's Primary Care slit lamp proves its value.

Unlike more sophisticated slit lamps for detailed diagnoses, Marco's Primary Care slit lamp has been streamlined for simplicity. Its operation can be learned in minutes. Yet its optical quality and fingertip control are the same as found in more expensive Marco instruments.

Marco's Primary Care slit lamp is available now from Marco producers of superior quality optical equipment for the past decade.

For additional information and complete specifications, return the coupon below.

Marco Equipment, Inc.
1316 San Marco Boulevard;
P.O. Box 10187;
Jacksonville, Florida 32207;
Call in Florida: 904-396-4210;
Nationwide Toll Free:
1-800-874-5274; Telex: 56209

MARCO

Marco; P.O. Box 10187; **Jacksonville, Florida 32207**
Please provide additional information and complete specifications about the Marco emergency slit lamp.

Company or Organization _____

Your Name _____ **Phone Number** _____

Title _____

Mailing Address _____

City and State _____ **Zip Code** _____

Proposed Amendments to the American College of Emergency Physicians Constitution and Bylaws

Prepared for the ACEP Council Meeting, September 7-8, 1985, Las Vegas, Nevada.

(Underlined information in the body of a resolution denotes a proposed addition; information lined out denotes a proposed deletion.)

RESOLUTION 1: Councillor Allotment

Whereas, The ideal and fairest form of representation is a bicameral system with one part being elected based on population (House of Representatives model) and one part being elected based on geography (Senate model); and

Whereas, The only elected representation from chapters in the American College of Emergency Physicians is based on population; and

Whereas, The cost of a bicameral system would be prohibitive for the American College of Emergency Physicians; therefore be it

RESOLVED, That Council membership be provided by a sliding scale based on population using the following formula: Each chapter shall elect one councillor for each 75 members for the first 300 chapter members, and each chapter shall elect one councillor for each 100 members for the next 400 members, and each chapter shall elect one councillor for every 150 members over 701; and be it further

RESOLVED, That the ACEP Constitution, Article V, Section 1, be amended to reflect the above resolution.

Submitted by: Hawaii Chapter

RESOLUTION 2: Submission of Resolutions

Whereas, The Council of the American College of Emergency Physicians must act on all resolutions submitted to it according to the ACEP Constitution and Bylaws; and

Whereas, Many resolutions are submitted to the Council after the mandated time frame (emergency resolutions) specified in the Constitution and Bylaws; and

Whereas, These last-minute resolutions tend to disrupt the orderly function of the formal Council meeting; therefore be it

RESOLVED, That the ACEP Constitution, Article V, Section 4, be amended to require that resolutions submitted after the time frame stated in the Constitution and Bylaws must be submitted to the Steering Committee for review at their meeting immediately prior to the annual Council meeting; and be it further

RESOLVED, That the Steering Committee will evaluate the need to submit the resolution to the Council during that year's annual meeting; and be it further

RESOLVED, That if the Steering Committee deems the resolution not to be of an emergency nature, it may postpone action on the resolution to the next annual meeting, and will consider the resolution formally submitted for the next annual meeting; and be it further

RESOLVED, That emergency resolutions submitted on the floor of the Council be handled as currently described in the Constitution and Bylaws.

Submitted by: Council Steering Committee

RESOLUTION 3: Board Action on Council Resolutions

Whereas, The American College of Emergency Physicians Constitution is unclear on what action the Board of Directors may take if it wishes to amend a Council resolution in order to add clarity to the language referred by the Council; and

Whereas, This has caused confusion when the Board has desired to amend a Council resolution; and

Whereas, Sometimes resolutions referred to the Board by the Council are unclear in intent and the Council officers are unable to interpret the specific actions requested by the Council; therefore be it

RESOLVED, That the ACEP Constitution, Article VI, Section 1, be amended to read: The Council shall have the right and power to advise and to instruct the Board of Directors regarding any matter that might affect the College. The Board of Directors shall be required to comply with and implement any and all resolutions, actions, or appropriations enacted by the Council, except that the Board of Directors may overrule or amend such instructions by a three-quarters vote of all of the Board of Directors provided that such an amendment shall not change the intent or basic content of the resolution. Such ~~overruling~~ actions to overrule or amend ~~should~~ shall include the ~~positions and~~ vote of each member of the Board of Directors and the position of the majority and be presented at the next meeting of the Steering Committee ~~Council prior to elections for the Board of Directors.~~ The Steering Committee may approve the language of the Board, in which case the resolution becomes complied with and implemented.

Further, if the Steering Committee disapproves of the language of the Board, the resolution is considered overruled and is returned to the Council at the next annual meeting.

The Board of Directors must respond to all questions presented by the Council within such time and manner as the Council shall determine, except that the Board of Directors may postpone action on Council resolutions for no more than one Board meeting.
Submitted by: Council Steering Committee

RESOLUTION 4: Council Officers as Voting Board Members

Whereas, The speaker and vice-speaker are important leaders of the College; and
Whereas, The speaker and vice-speaker currently attend all Board meetings but are without a vote or the privilege of making motions; and
Whereas, Participation by the speaker and vice-speaker in Board activity is essential to the operation of the College; therefore be it
RESOLVED, That the ACEP Constitution, Article VII — Officers and Board of Directors, Section 2 — Board of Directors, be amended by addition to read: The management and control of the College shall be vested in the Board of Directors, subject to the restrictions imposed by the Constitution and Bylaws. The Board shall consist of 12 elected members ~~and~~ plus the immediate past president, except that the Board may consist of only 12 elected members when the immediate past president serves as such within his term as an elected Board member. Additionally, the speaker and vice-speaker shall serve as ex officio members of the Board with full voting privileges. If a member of the Board of Directors is elected to the office of president-elect in his final year of his elected Board of Directors' term of office, then he shall also be a member of the Board in his term as President and past president. In no instance may an elected member of the Board of Directors sit as a member of the Council, and if a councillor should be elected to the Board of Directors, he shall forfeit his office in the Council immediately and the vacancy shall be filled as provided in the Bylaws.
Submitted by: Council Steering Committee

RESOLUTION 5: Speaker as Voting Board Member

Whereas, The Council of the American College of Emergency Physicians may be the most important advisory and decision-making organization in the American College of Emergency Physicians; and
Whereas, The Council lacks voting representation on the Board of Directors; and
Whereas, The speaker of the Council is elected by the Council to represent the Council in matters before the Board; therefore be it
RESOLVED, That the speaker of the Council be a full voting member of the American College of Emergency Physicians Board of Directors; and be it further
RESOLVED, That the ACEP Constitution, Article VII, Section 4, be amended to reflect the above resolution.
Submitted by: Hawaii Chapter

RESOLUTION 6: Speaker on Executive Committee

Whereas, The ACEP Constitution specifies that there are six officers of the College — President, vice-president, president-elect, secretary-treasurer, speaker, and vice-speaker; and
Whereas, The ACEP Constitution specifies that the Board of Directors may appoint an Executive Committee consisting of the President, president-elect, secretary-treasurer, vice-president, and immediate past president to act on behalf of the Board subject to ratification by the Board at its next meeting; and
Whereas, The ACEP Bylaws states that the speaker shall strive to inform the councillors of the activities of the College; and
Whereas, The speaker should be a member of the Executive Committee like other officers of the College; therefore be it
RESOLVED, That the ACEP Constitution, Article VII — Officers and Board of Directors, Section 4 — Executive Committee, be amended by addition to read: The Board of Directors may appoint an Executive Committee consisting of the President, president-elect, secretary-treasurer, ~~the~~ vice-president, ~~and the~~ past president, and speaker. The Executive Committee shall have the authority to act on behalf of the Board subject to ratification by the Board at its next meeting.
Submitted by: Council Steering Committee

RESOLUTION 7: *Robert's Rules of Order*

Whereas, *Robert's Rules of Order* is more widely published and understood than *Sturgis, Standard Code of Parliamentary Procedure*, which is currently the parliamentary authority for meetings of the College and
Whereas, one previous Council meeting lacked a parliamentarian because none familiar with *Sturgis* was available; therefore be it
RESOLVED, That Chapter X, Section 5, of the ACEP Bylaws be amended by the substitution of *Robert's Rules of Order* for *Sturgis, Standard Code of Parliamentary Procedure*.
Submitted by: Thomas Stair, MD

Abstracts of the 1985 Scientific Assembly, American College of Emergency Physicians

*[**Editor's Note:** The following 12 abstracts will be presented at the ACEP Scientific Assembly in Las Vegas on Tuesday, September 10, from noon to 2 pm and Wednesday, September 11, from noon to 2 pm. The Scientific Forum is scheduled to accommodate a question and answer period following each presentation. All presentations will be eligible for the $1,000 Micromedex Award for Best Original Scientific Paper, and all resident presentations are eligible for the $250 Annals Award for Best Resident Paper.]*

1 Regional Blood Flow During External CPR Following Hypothermia-Induced Cardiac Arrest

PA Maningas (presenter), LR DeGuzman, SJ Hollenbach, KA Volk, RF Bellamy / Division of Combat Casualty Care, Letterman Army Institute of Research, Presidio of San Francisco, California

Controversy still remains over the efficacy of CPR in the pulseless, hypothermic patient. We evaluated organ blood flow produced by closed-chest CPR in 15 chronically instrumented, immature gilt swine weighing between 19 kg and 27 kg. In 8 animals, CPR followed normothermic KCl-induced cardiac arrest (1 mEq/kg). Seven animals underwent surface cooling at a rate of 5 C to 6 C/hr until cardiac arrest occurred. The mean temperature at the time of arrest was 22 ± 2 C, with a mean cooling time of 169 ± 47 minutes. Chest compressions were delivered transversely by a pneumatic chest compression device (Michigan Instruments, Inc) at a rate of 60 strokes/minute and a piston stroke of 2 inches with compression lasting one-half of the massage cycle. Approximately 4×10^6 15 u radiomicrospheres labeled with ^{103}Ru, ^{46}Sc, ^{51}Cr, or ^{141}Ce were injected during the unanesthetized, basal state and 5 and 20 minutes following the initiation of CPR. After 5 minutes of hypothermic CPR, cardiac output and cerebral and myocardial blood flows were (mean ± SD): 15.3 ± 7.5 mL/min/kg, 0.16 ± 0.11 mL/min/g, and 0.20 ± 0.15 mL/min/g, respectively. These flows were 50%, 55%, and 31% (respectively) of those produced during CPR in normothermic animals, and 7%, 15%, and 8% (respectively) of the flow produced in the unanesthetized, prearrest state. Blood flow during hypothermic CPR did not change significantly over time. During normothermic CPR, however, cardiac output and cerebral and myocardial blood flows decreased so that at 20 minutes there were no significant differences from those values obtained in hypothermic animals. The tolerance of the hypothermic brain and heart to the low perfusion state produced during external chest compression is undefined. These low organ blood flows may meet sufficiently the reduced metabolic demands of the hypothermic brain and heart. Studies are now in progress to evaluate the effect of CPR versus no CPR on resuscitability and neurologic outcome following prolonged hypothermic circulatory arrest.

2 The Arteriolar Alveolar Gradient and High-Yield Factors for Ventilation Perfusion Scanning in Young Adults

A Gravett (presenter), M Wenman, J Clinton, E Ruiz / Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota

The exclusion of pulmonary embolism (PE) in young adults with chest pain is difficult. Two hundred ventilation/perfusion (V/Q) scans in patients less than 40 years old were reviewed. Charts were selected at random from the V/Q files of the previous 15 years. Thirty-one historical, clinical, and laboratory values were evaluated. The alveolar-arteriolar (A-a) gradient was evaluated as a screening test prior to V/Q scanning. Intermittent chest pain, pain resolving prior to V/Q scan, or respiratory prodrome were seen only in patients without PE (36 of 182). Of patients with PE, 50% (9 of 18) had a history of previous PE, DVT, or immobilization, versus 12% (22 of 182) of patients without PE ($P < .001$). Of patients with PE, 50% (9 of 18) had signs of phlebitis on examination, versus 18% (33 of 182) of those without PE ($P < .01$). An abnormal chest radiograph showing infiltrate or effusion was present in 50% of patients (9 of 18) with PE and 90% of patients (25 of 28) with pneumonia. Effusions or infiltrates were seen in only 6.5% of the remaining patients (10 of 154). These differences were statistically significant ($P < .001$). The incidence of effusion was not statistically different between pneumonia and PE. Infiltrates, however, were most likely found in pneumonia ($P < .001$). The A-a gradient was not found to be discriminatory for PE in the absence of other findings. Higher A-a gradients (> 45) were more suggestive of serious pathology (PE or pneumonia) than of less serious illness ($P < .01$). High A-a gradients, however, occurred in all diagnostic categories. The elevated A-a gradient is not by itself an indication for V/Q scanning in the young adult. The A-a gradient should accompany a history of PE/DVT, immobilization, evidence of phlebitis, or abnormal chest radiograph before V/Q scanning is considered. This combination would have detected 94% of PE (17 of 18) in our series.

3 The Effect of Graded Doses of Epinephrine on Regional Brain Blood Flow During Cardiopulmonary Resuscitation

CG Brown (presenter), HA Werman, RL Hamlin, J Hobson, J Ashton / Division of Emergency Medicine, Department of Veterinary Physiology and Pharmacology, and Department of Preventive Medicine, Ohio State University, Columbus, Ohio

We recently reported that 0.2 mg/kg of epinephrine (E) administered peripherally following a 10-minute cardiac arrest in a porcine model significantly increased brain blood flow compared to a "standard" dose of 0.02 mg/kg. Following 0.2 mg/kg of E during CPR, blood flow increased significantly, and ranged from 52% of baseline to the cerebral cortex to 93% of baseline to the cervical cord. In our current study, using the same experimental model, we sought to determine whether the peripheral administration of 2.0 mg/kg of E during CPR could further improve regional brain blood flow over that seen with 0.2 mg/kg of E. Eight swine weighing 16.8 to 20.2 kg were randomized to receive either CPR plus

0.2 mg/kg of E or CPR plus 2.0 mg/kg of E through a peripheral IV line. All animals were instrumented for cerebral blood flow (CBF) measurements using radioactively labeled tracer microspheres. Baseline measurements were made during normal sinus rhythm (NSR). Ventricular fibrillation (VF) then was induced. Following 10 minutes of VF, CPR was begun with a pneumatic compressor (Michigan Instruments, Inc). CBF was measured during CPR. At the end of 3 minutes of CPR, E was administered. One minute after E administration CBF was measured again. A Wilcoxon rank sum test was used to compare blood flow between the two groups. P values $< .05$ were considered statistically significant. The regional CBFs during CPR + E are reported as a percentage of NSR blood flow. The regional CBFs for the 0.2-mg and 2.0-mg groups, respectively, were: left cerebral cortex, 0.47 versus 0.50; right cerebral cortex, 0.48 versus 0.50; cerebellum, 0.70 versus 1.03; midbrain/pons, 0.86 versus 0.88; medulla, 0.78 versus 1.34; and cervical spinal cord, 0.93 versus 1.21. All comparisons between groups for each organ measured had P values $> .05$. While there was no statistically significant improvement in regional brain blood flow seen with this higher dose of E, there was a trend in our data that demonstrated improved blood flow to more caudal CNS structures. Our preliminary report suggests that higher doses of E may further improve CBF. Further studies with larger sample sizes will be required to verify this statistically.

4 The Relationship of Hemodynamic Parameters to Neurologic Outcome from Cardiac Arrest in the Animal Model

JC Brillman (presenter), AB Sanders, CW Oito, H Fahmy, S Bragg, GA Ewy / Sections of Emergency Medicine and Cardiology and the Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, Arizona

Several studies in the literature have demonstrated that specific hemodynamic parameters, the aortic diastolic and myocardial perfusion pressures, are correlated with resuscitability from cardiac arrest in the animal model. The relationship of these pressures to 24-hour survival and neurologic deficit is, however, unknown. Therefore a study was done to determine the correlation of hemodynamic parameters to 24-hour neurologic outcome. Ventricular fibrillation was electrically induced in 18 dogs. After 3 minutes standard CPR was begun. Dogs were given phenylephrine or epinephrine at 9 minutes, and defibrillation was attempted at 12 minutes. Dogs underwent hemodynamic monitoring and pharmacologic support during a critical care period for 90 minutes. At 4, 8, 12, and 24 hours a standard neurologic examination was performed and deficit scores were assigned. Fourteen of eighteen dogs were initially resuscitated, and 10 lived for 24 hours following arrest. Aortic systolic pressures were correlated positively with improved neurologic outcomes ($r = .64$, $P < .05$). This relationship was linear, and no stratification could be made whereby achievements of specific pressures would result in a good neurologic outcome. Other variables that could not be correlated with improved neurologic survival included 1) diastolic pressure, mean arterial pressure, myocardial perfusion pressure, or central venous pressures prior to defibrillation; and 2) all hemodynamic variables during the critical care period after defibrillation. In conclusion, the aortic systolic pressure was correlated positively with improved neurologic outcome in this animal model of cardiac arrest. Whereas previous efforts to improve resuscitability from cardiac arrest centered on improvements in the aortic diastolic and myocardial perfusion pressures, there may be a need to focus on drugs or techniques that improve systolic pressures as well.

5 Digital Hydrofluoric Acid Burns: Treatment with Intraarterial Calcium Infusion

MV Vance, SC Curry, DB Kunkel, PJ Ryan / Central Arizona Regional Poison Management Center, St Luke's Medical Center, Phoenix, Arizona

Hydrofluoric acid (HF) produces a unique chemical burn due to tissue penetration by fluoride ion. Fluoride ion interferes with calcium activity in a variety of cell membranes and calcium-dependent processes, resulting in severe pain and deep tissue destruction. The currently accepted methods of treating HF burns include application of topical soaks or ointments with calcium or magnesium salts for minor burns and local injection of calcium gluconate for more severe burns. Digital burns also may require nail removal and direct injection into the nail bed. We present a series of patients with moderate to severe HF burns involving one or more fingers who were treated with selective intraarterial calcium infusion of diluted (1.66%) calcium salts. All patients had excellent relief of symptoms and marked improvement of the burn lesions following one to three four-hour infusions of calcium chloride or calcium gluconate. Only one patient required subsequent surgical intervention for grafting of a full-thickness burn, and one patient developed transient spasm at the site of percutaneous arterial line insertion. Intraarterial calcium infusion for the treatment of HF burns of the fingers provides many therapeutic advantages, including elimination of painful calcium injection directly into fingertips, avoidance of such debilitating procedures as fingernail removal, and assurance that all affected cells are receiving adequate amounts of calcium to replenish depleted stores and to "neutralize" remaining free fluoride ion.

6 Activated Charcoal Before Syrup-of-Ipecac-Induced Emesis

GE Freedman, EP Krenselak, S Pasternak (presenter) / Mercy Hospital, Pittsburgh Poison Center, Children's Hospital of Pittsburgh, and the Center for Emergency Medicine of Western Pennsylvania, Pittsburgh, Pennsylvania

It is commonly stated that activated charcoal will prevent the emetic effect of syrup of ipecac. Although not clinically substantiated, this view has become dogma. A study was performed to observe the effects of activated charcoal on the emetic properties of syrup of ipecac and to develop an efficient protocol for treatment of the nonobtunded overdose patient. Ten volunteers, who ingested 2.6 g aspirin orally as a marker drug, were administered 60 cc syrup of ipecac plus 480 cc water through a nasal gastric tube. Five minutes later, a 50-g aqueous charcoal slurry was infused through the tube, the tube was removed, and the subjects were observed for emesis. The subjects acted as their own controls and were subsequently administered only 2.6 g aspirin orally. Eight of ten subjects (80%) had a significant emetic response, the other two had nausea without emesis. Serum salicylate levels measured two hours after salicylate ingestion showed an average reduction of 57% from control in the subjects with emesis (8 of 10) compared to an average reduction of 48% in the subjects without emesis (2 of 10). Our study illustrates that activated charcoal may not prevent the emetic effects of syrup of ipecac. The protocol developed allows the very early administration of activated charcoal compared to conventional teaching, and has been shown to be effective in reducing marker drug levels with or without emesis.

7 Comparison of the Intraosseous and Intravenous Routes of Diazepam Administration for Pentylenetetrazol-Induced Seizures

WH Spivey, HD Unger (presenter), RM McNamara, CM Luthers / Departments of Emergency Medicine and Pharmacology, Medical College of Pennsylvania, Philadelphia, Pennsylvania

This study examines an alternative route of administration for diazepam in the control of seizure activity. The intraosseous route (IO), through the bone, is much simpler than IV access and

may be used in children and infants during status epilepticus when IV access is not available. The IO and IV routes of diazepam administration were compared in a pentylenetetrazol (PTZ) seizure model. Ten domestic swine weighing 14 to 19 kg were anesthetized with ketamine 20 mg/kg IM and alpha-chloralose 25 mg/kg IV and were ventilated with a respirator on 35% O_2. Blood pressure and lead II ECG were monitored throughout the experiment. Electrocortical activity was recorded directly from the brain with platinum electrodes. All animals were given PTZ 100 mg/kg IV to induce seizure activity, and they received diazepam 0.1 mg/kg IV 1 minute after the onset of seizure through a peripheral IV (n = 5) or through an 18-gauge needle in the proximal tibia IO (n = 5). Blood samples were drawn for determination of diazepam levels at 1, 2, 5, 10, 15, and 20 minutes after diazepam administration. Control heart rates and mean arterial blood pressure were similar for the two groups: 240.6 ± 11.1 and 238.7 ± 7.0 beats/minute, and 128.6 ± 12.0 and 127.2 ± 8.3 mm Hg for IV and IO, respectively. The time to onset of seizure was 20.2 ± 3.02 seconds and 16.4 ± 2.5 seconds for the IV and IO routes, respectively ($P > .05$). IV diazepam suppressed seizure activity in all IV animals in 38.4 ± 10.8 seconds, while IO diazepam stopped it in 4 IO animals in 53.2 ± 29.3 seconds. One IO animal had increased ictal activity for 12 minutes. Serum diazepam levels (ng/mL) and standard error for the IV and IO groups were as follows: 1 minute, 260 ± 97.2, 190 ± 50.7; 2 minutes, 195.0 ± 41.0, 172.5 ± 42.7; 5 minutes, 187.5 ± 24.3, 153.3 ± 24.0; 10 minutes, 123.3 ± 12.0, 153.3 ± 37.1; 15 minutes, 130.0 ± 17.3, 146.7 ± 13.3; and 20 minutes, 120.0 ± 15.8, 145.0 ± 28.7, respectively. An analysis of variance revealed no statistical difference in the 2 groups; 105 ng/mL or greater is therapeutic. The data show the IO route to be a rapid and effective method of administering diazepam and suppressing seizure activity during status epilepticus when IV access is not readily available.

8 Effect of Volume on the Endotracheal Absorption of Lidocaine

SE Mace. Mount Sinai Medical Center, Cleveland, Ohio

Lidocaine was given endotracheally in a dose of 2 or 4 mg/g to 15 dogs. Blood lidocaine levels were drawn at 5, 15, 30, and 60 minutes after administration of lidocaine. Endotracheal lidocaine was given either as a dilution with normal saline (a 1:1 dilution of lidocaine and normal saline) or undiluted (Group 1, no dilution; Group 2, dilution with normal saline). Significantly higher blood lidocaine levels were obtained in the dilution group in all the time periods and with either dose (2 or 4 mg/kg) ($P < .001$). Mean blood lidocaine levels (μg/mL) at 5 minutes were (2 mg/kg dose) Group 1 0.64, Group 2 3.4; and (4 mg/kg dose) Group 1 1.4, Group 2 6.2 ($P < .001$). The same dose of lidocaine was diluted with normal saline to a total volume of 3 mL, 6 mL, 12 mL, or 25 mL of fluid. Four additional dogs received all four dilutions of endotracheal lidocaine on different days. In each of the four dogs, blood lidocaine levels were significantly different depending on the total amount of fluid given ($P < .001$). In one dog at the same endotracheal lidocaine dosage, blood lidocaine levels (at 5 minutes) varied from 2 to 9.1 depending on the amount of normal saline administered with the endotracheal lidocaine. This study suggests that 1) higher blood lidocaine levels are achieved and maintained longer when lidocaine is diluted with normal saline than when it is given undiluted, and 2) there may be a maximal volume at which the highest blood lidocaine level is obtained without a corresponding change in respiratory function.

9 Incidence of "Secondary Drowning" After Saltwater Immersion

ED Pratt (presenter), BE Haynes. Department of Emergency Medicine, Harbor UCLA Medical Center, Torrance, California

The reported incidence of delayed pulmonary and CNS symptoms after submersion, so-called "secondary drowning," is derived from retrospective analysis, frequently of patients who had established pulmonary pathology. Characterizing subsets of victims could reduce unnecessary hospitalization of some patients and promote vigorous evaluation of those at risk. We prospectively evaluated a large saltwater beach population. Swimmers were eligible for the study if they exhibited coughing, cyanosis, loss of consciousness in the water, tachypnea, or vomiting, or if they requested medical attention after submersion. Among an estimated 33,170,000 beach visits during one summer, there were 5,474 rescues (any contact with a bather), with 53 patients entered in the study. Thirty-two (60%) of the victims were released on the beach, and none of the 27 victims followed up by telephone required medical care after the initial episode. Twenty-one patients (40%) were transported to a hospital for further evaluation. Ten presented on the beach with findings mandating ICU admission. The other 11 patients (21%) had minimal symptoms when they emerged from the water. Three developed severe symptoms in the ED mandating ICU admission, while 8 were observed in the ED or as inpatients without sequelae. Four of the 8 had an abnormal chest radiograph, acidosis, or hypoxemia despite minimal clinical findings. The need for these studies in the ED is reinforced. Study limitations include the small final patient population and lack of laboratory studies on all patients. We conclude that experienced lifeguards can effectively triage submersion victims, that mild symptoms progress to marked distress in only a few patients, and that patients who develop delayed distress do so within a few hours. ED observation for 4 to 6 hours could screen effectively for those patients requiring inpatient therapy.

10 Appendicitis in the Elderly: A Diagnostic Challenge

SR Klein, E Layden (presenter), JF Wright, RA White. Department of Surgery, Harbor UCLA Medical Center, Torrance, California

Acute appendicitis is uncommon in patients more than 60 years old, but this age group accounts for a significant proportion of the morbidity and mortality related to this entity. To establish a profile of the disease in this population, the charts of 94 patients age 60 to 95 with pathologically proven acute appendicitis were reviewed. Sixty-two percent were in their 60s, and 20% were more than 80 years old. Thirty-one percent had symptoms more than 48 hours prior to presentation. The most frequent presenting symptom was abdominal pain (93%), but only 66% had right lower quadrant localization. At presentation, 70% of patients had fever exceeding 37.2 C, and 83% had leukocytosis (WBC count > 10,000). Operation was carried out within 24 hours of presentation in 81%, but was delayed more than 48 hours in 15% as a result of an incorrect admitting diagnosis in all cases. The overall incidence of perforation was 62%. This was related directly to the duration of the illness, and occurred in 84% of those with symptoms for more than 48 hours, compared to an incidence of 20% in those with symptoms present less than 24 hours. The overall complication rate was 50%, which rose to 75% in those with perforation. The most common complication was wound infection. Four patients (4%) died, three of them having had a delay in operation of more than 48 hours; all had perforation at surgery. We conclude that delay in the patient seeking medical care or the physician arriving at the prompt diagnosis and proceeding with early surgical intervention are the factors related to the elevated morbidity and mortality observed in acute appendicitis in the elderly.

11 Fixed Atlanto-Axial Rotatory Subluxation: A Radiographic Finding of Questionable Clinical Significance

S Lee (presenter), SM Joyce, J Seeger, R Hanson, E Criss · Section of Emergency Medicine and Department of Radiology, University of Arizona Health Sciences Center, Tucson, Arizona

Atlanto-axial rotatory subluxation is a finding occasionally noted on cervical spine radiographs obtained following head and neck trauma. Atlanto-axial subluxation produces an asymmetry of the lateral masses of C-1 relative to the odontoid process on the AP open-mouth view. Persistent asymmetry, not correctable by a 15° head rotation, has been used as the criterion to define fixation of atlanto-axial subluxation. Chronic neck pain, occipital neuralgia, and torticollis requiring neurosurgical intervention have been documented in cases when atlanto-axial subluxation becomes fixed. The clinical significance of rotatory subluxation with fixation in patients with minimal or no symptoms, however, is uncertain. Atlanto-axial subluxation is seen during normal head rotation; thus it is possible that subluxation on the AP view actually may be due to improper positioning. Such positional subluxation, however, would not be expected to be fixed. A study was performed to evaluate the effect of positioning on the atlanto-axial relationship and the ability to correct asymmetry by rotation. Eleven normal volunteers without recent neck trauma, neck pain, or limitation of neck motion were evaluated with the following AP open-mouth views: 1) without tilt or rotation (neutral); 2) 15° rotation in each direction; 3) 15° head tilt to the right; and 4) right rotation with right tilt and left rotation with right tilt (the "cock-robin" position). Six normals demonstrated apparent rotational asymmetry in the neutral position despite proper positioning. No predictable change in the atlanto-axial relationship was produced by any of the manipulations described. Two normal subjects fulfilled the radiographic criterion for fixed atlanto-axial subluxation, asymmetry not corrected by rotation. The radiographic finding of atlanto-axial rotatory subluxation is common and is not in itself abnormal in the absence of clinical findings. In addition the criterion of fixation, asymmetry uncorrected by rotation, appears to be inadequate. Patients with atlanto-axial subluxation should be evaluated further relative to their clinical findings.

12 An Analysis of Medical Care at Mass Gatherings

AB Sanders (presenter), E Criss, P Steckl, HW Meislin, J Raife, D Allen · Section of Emergency Medicine, University of Arizona Health Sciences Center, Tucson, Arizona

Emergency medical care at public gatherings is haphazard at best, and dangerous at worst. Arizona ACEP, through the Chapter Grant Program, studied the level of medical care provided at public gatherings in order to develop standards for emergency medical care at mass gatherings. The study consisted of the following: 1) a survey of medical care at 14 facilities providing events for the public (more than 1,000 people in attendance). Questions were asked regarding the nature of the event, number of people, density of seating, predominant age group, availability and checks for liquor and drugs, indoor versus outdoor event, and the level and facilities for medical care; and 2) a retrospective and prospective survey of injuries occurring at mass gatherings during a one-year period was done. The results of these surveys showed a wide variation of medical care provided at mass events. Of the 490 medical encounters reviewed, 52.2% were within the realm of care of paramedics but not basic EMTs alone. The most common injuries/illnesses were lacerations, sprains, headaches, and syncope. Problems noted included 1) poor documentation and record keeping of medical encounters; 2) a tendency for prehospital care personnel to make medical evaluations without transport or medical control; and 3) frequently inadequate communication to make the public aware of the availability of medical care. Based on this survey and a literature review, standards for medical care at mass gatherings were determined using an objective-oriented approach. It is our position that event organizers have the responsibility of ensuring the availability of emergency medical services for spectators and participants. Mandatory medical care objectives for all events include provision of the following: 1) basic first aid and life support within 4 minutes; 2) advanced life support within 8 minutes; and 3) evacuation to a definitive care facility within 30 minutes of illness or injury. Optional objectives include 1) medical evaluation and treatment for nonemergency problems, and 2) triage and medical evaluation of a presenting complaint. Guidelines on how these objectives can be met by sponsors are provided.

CORRESPONDENCE

Rocky Mountain High

To the Editor:

In the mountains of Colorado, July and August are normally the peak months for finding mushrooms. A family was poisoned when they ate an unusual variety of a common species of poisonous mushroom.

The Rocky Mountain Poison Center was called concerning three patients who had eaten some white mushrooms five to six hours earlier. The patients were a 41-year-old man, his 10-year-old son, and a 9-year-old neighbor. The boys had collected "meadow mushrooms" from the grass- and pine-covered areas around their mountain house. The man had eaten two mushrooms (approximately five inches tall with a four- to five-inch cap); the 10-year-old ate one and one-half to two. The 9-year-old ate one to one and one-half mushrooms but had peeled portions of the cap. The mushrooms had been fried.

Within an hour the three felt confused and disoriented. Two to three hours postingestion the man felt very confused. The adult and the 10-year-old reported muscle twitching, which was most pronounced in the arms and legs.

Five hours after ingestion paramedics were summoned, and the patients were flown to a local hospital. At that time their symptoms were tingling of the extremities, vertigo, ataxia, confusion, and disorientation that they described as hallucinations.

The man and the 10-year-old became much more symptomatic than did the 9-year-old, who had peeled the mushroom cap. The adult had a pulse of 110 and was flushed, slightly sweaty, and nauseated. None of the patients vomited. The three became very sleepy and repeatedly fell into sleep from which they could be aroused easily. The only treatment given was supportive care and observation; emesis, charcoal, or catharsis was not performed. The patients were discharged nine to ten hours after ingestion, still sleepy but easily arousable. This feeling continued into the next day. A sample mushroom was sent, but because of its poor condition it could not be identified positively. We reviewed the site of the mushrooms the next day and found both an *Agaricus* species (edible) and *Amanita pantherina*. Identification was accomplished with the help of staff from the Denver Botanic Gardens. The mushrooms were not analyzed for their isoxazole content.

Amanita pantherina usually is described as having a brown cap, pointed warts, and a single, well-formed annulus (ring). In the Pacific Northwest this mushroom is known to hybridize with *Amanita gemmata*, resulting in colors ranging from dark brown to light yellow.[1] The variety found by the patients on the east slopes of the Rocky Mountains was nearly white and wartless. To amateur eyes the pale pink gills of young agarics appeared very similar to the white gills of the *Amanita pantherina*. In addition, the patients did not recognize the clinging annulus and volva characteristic of the *Amanita species*.

Amanita pantherina is known to contain the toxic isoxazole derivatives ibotenic acid and muscimol, as well as stizolobic and stizolobinic acid. Ibotenic acid is not stable, and it degrades on drying to muscimol, which is five to ten times as potent. *Amanita pantherina* loses most of its potency on drying.[2]

These agents act primarily on the CNS and most likely compete with the neurotransmitter GABA to produce symptoms including irrational behavior, alcohol-like inebriation, delirium, and deep sleep.[3] When *Amanita pantherina* is used as a hallucinogen, individuals report hearing voices, seeing visions, exhibiting inappropriate behavior, and having a need for physical activity. Macroposia is another reported delusion. In other reported cases in which cooked *Amanita pantherina* was ingested, impaired vision, dizziness, loss of coordination, inability to think or speak clearly, and hysteria were noted. A death was reported in a man with a weak heart.[4]

Samples of typical *Amanita pantherina* contain 0.42% dry weight of the two isoxazoles. Hybrids may contain 0.02% to 0.35% of these derivatives.[5] Concentrations of these toxins vary by growing conditions and season of growth.[6]

A dose of 20 mg ibotenic acid, tested on a man, produced only flushing and migraine headaches. Five milligrams of muscimol produced slight drowsiness; 10 mg muscimol produced, within 90 minutes, mild symptoms of intoxication, including slight muscle twitching but no hallucinations. Fifteen milligrams of muscimol produced a full-blown intoxication.[7]

Amanita pantherina has been used as food, particularly in the Pacific Northwest. The skin is peeled from the cap of the mushroom, it is parboiled once or twice, and the water is discarded. Because the highest concentration of isoxazole is in the skin of the cap and the toxins are water soluble, this process may remove most or all of the toxic compounds.[8] This may be why the 9-year-old, who peeled his mushroom, had less severe symptoms.

Several types of mushroom poisoning have onset ranging from 20 minutes to two hours, and treatment recommendations require differentiation. The muscarine group typically exhibits cholinergic symptoms of salivation, lacrimation, and perspiration. Treatment is atropine. When hallucinations and disorientation are present, the primary suspect is the psilocybin group of mushrooms. The third type, including a mushroom that produces a disulfiram-like reaction, may cause nausea and vomiting during the first two hours after ingestion.

Some other cases in the third type may exhibit slight peripheral anticholinergic symptoms; these cases may involve the isoxazole compounds. Patients may appear intoxicated, have twitching muscles and lack of coordination, and may exhibit euphoria and hyperkinetic activity. If discovered early, patients may be decontaminated by emesis and activated charcoal. If the toxic substances have been absorbed, the patient should be placed in a low-stimulus environment to be observed for rare serious CNS depression. This simple measure usually is all that is required. Respiratory failure is very unlikely. Rarely anticholinergic symptoms may be pro-

nounced and physostigmine salicylate (1-2 mg IV) may be considered. Physostigmine should be used only in severe cases.

Because mild peripheral anticholinergic symptoms may occur, atropine, which is often given for another two-hour-onset mushroom poisoning caused by muscarine, is contraindicated and will exacerbate the symptoms.[4] The two most common *Amanitas* mushrooms are *A pantheria* and *A muscaria*. The "muscaria" in *A muscaria* may lead one to believe that significant amounts of muscarine are present in these mushrooms. This is not the case.

Gathering wild mushrooms for consumption is always risky when done by amateurs. In our case, two school-age boys gathered mushrooms that they and another family member subsequently ingested. Earlier that week they had gathered several *Agaricus* species mushrooms and consumed them without negative effects. The patients failed to recognize this light-colored variety of a normally brown-to-yellow mushroom.

David G Spoerke, MS, RPh
Barry Rumack, MD
Rocky Mountain Poison Center

Susan E Spoerke, MD
Denver Clinic Medical Centers

Denver, Colorado

1. Miller OK Jr: *Mushrooms of North America*. New York, EP Duttion and Company, Inc, 1979, p 31.

2. Chilton WS, Ott J: Toxic metabolites of Amanita pantherina, A cothurnata, A muscaria and other Amanita species. *Lloydia* 1976;39:150-157.

3. Lincoff G, Mitchell DH: *Toxic and Hallucinogenic Mushroom Poisoning*. New York, Van Nobstrand Renhold Company, 1977, p 77-99.

4. Hotson JW: Mushroom poisoning at Seattle. *Mycologia* 1934;26:194-195.

5. Tyler V Jr: Chemotoxonomy in the basidionmycetes, in Peterson RH (ed): *Evolution in The Higher Basidiomycetes*. Knoxville, University of Tennessee, 1971.

6. Benedict RG, Tyler VE, Brady LR: Chemotoxonomic significance of isoxazole derivatives in Amanita species. *Lloydia* 1966;129:333-342.

7. Waser PG: The pharmacology of Amanita muscaria, in Efron DH (ed): *Ethnopharmacologic Search for Psychoactive Drugs*, publication no. 1645. Washington DC, US Public Health Service, 1967, p 419-439.

8. Rumack BH, Salzman E: *Mushroom Poisoning: Diagnosis and Treatment*. West Palm Beach, Florida, CRC Press, Inc, 1978, pp 110-115.

Factitious Arrhythmia

To the Editor:

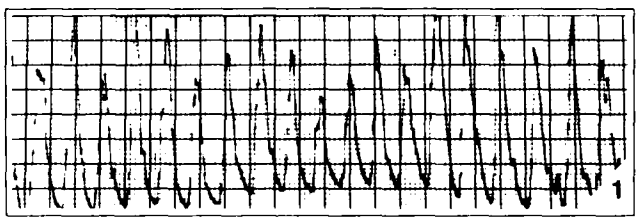
We describe an interesting case in which critical analysis of a piece of clinical information, the cardiac monitor rhythm strip, convincingly demonstrated the benign nature of a patient's presentation. This occurred in a setting in which one might easily accept a very different interpretation conferring a serious diagnosis on the patient.

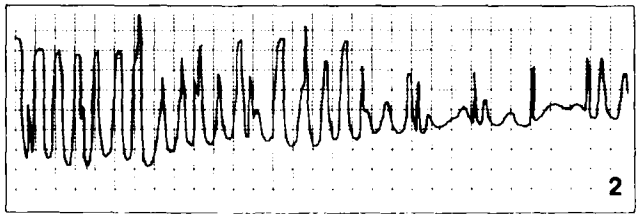
The Worcester City Ambulance Service called our emergency department (ED) requesting medical control for a 26-year-old man complaining of chest pain. The patient was awake and communicating when encountered by the paramedic team. Vital signs at the scene were as follows: palpable blood pressure, 90 mm Hg; pulse, 120; and respirations, 20. Treatment rendered prior to arrival in the ED consisted of intravenous D_5W at KVO, nasal oxygen, and monitoring. On arrival approximately five minutes later, the patient complained of a dull, pressing pain in the chest, radiating to the neck and left arm and associated with shortness of breath, nausea, and palpitations. He stated that he recently had been hospitalized for chest pain and that he had signed out against medical advice several hours prior to presentation at our ED.

The medical history was significant for a rhythm disturbance that was "studied" in Texas and was thought to be "of a ventricular nature." He was treated with quinidine and showed an empty prescription bottle bearing his name. Cardiac risk factors included a two-pack-per-day smoking history and a family history strongly positive for early myocardial infarction.

Physical examination revealed a well-nourished, well-developed man in moderate distress secondary to pain. His right hand was over the precordium. Vital signs were as follows: blood pressure, 140/90 mm Hg, without orthostatic changes; pulse, 105; and respirations, 20. With the exception of venous "track marks" on the upper extremities, the remainder of the physical examination was normal. Routine blood work, arterial blood gases, and a chest radiograph were normal. A 12-lead electrocardiogram showed sinus rhythm at a rate of 95 and a normal pattern.

The patient was placed on a cardiac monitor. Initial treatment with nasal oxygen and sublingual nitroglycerine 1/150





g failed to lessen the patient's symptoms. His cardiac monitor showed a transient rhythm disturbance (Figure 1). This lasted for three to five seconds and immediately brought the staff back to his bedside. He complained of increasing pain at this time. There was no loss of consciousness and no change in the vital signs taken immediately following this self-limited episode. Given the rate of 170 and the regularity of this rhythm, a diagnosis of nonsustained ventricular tachycardia was entertained. Similar episodes followed, never associated with changes in vital signs, and always resolving as a nurse or physician approached the bedside.

Closer examination of a second rhythm strip (Figure 2), in consultation with a cardiologist, revealed two interesting findings. Toward the end of the strip, under the #1, is what appears to be a ventricular couplet closely following a sinus beat. The first complex occurs over the early portion of the ST segment during the absolute refractory period of ventricular myocardium and cannot represent ventricular depolarization. Similarly the R-R interval between the apparent PVC and sinus beat occurring under #2 is well below the briefest expected ventricular absolute refractory period. Thus, for physiologic reasons, the aberrant activity cannot be ventricular depolarization. There are numerous sharp spikes superimposed on the episode of apparent nonsustained ventricular tachycardia. These spikes march out perfectly (arrows, Figure 2) with the patient's underlying sinus rhythm, further indicating the factitious nature of his rhythm disturbance.

When reassured that it has been determined that the monitor changes were artifactual and did not represent a danger, the patient refused further examination and signed out against medical advice. Area hospitals were notified to be aware of similar presentations by the same individual. It was later ascertained that the patient was indeed admitted to an outlying hospital for chest pain on the day prior to his presentation to us. His workup was similarly negative and included a quinidine level of less than 1.5 μg/mL. He had received a total of 14 mg intravenous morphine sulfate prior to signing out against medical advice the following morning.

We hypothesize that while being monitored without medical staff in close attendance, the patient manipulated his monitor leads to simulate the arrhythmia. It was possible to do this at bedside, creating a pattern identical to those shown. His initial hypotension can be explained by self-administration of nitrates just prior to the arrival of the ambulance. Amyl nitrate (widely available on the street) may be implicated given the pronounced, short-lived nature of the hypotension and reflex tachycardia for which alternative physiologic explanations are lacking in this patient.

This case illustrates one example of the sophisticated techniques employed by malingering patients presenting to an ED. Careful analysis of appropriate laboratory studies may, at times, permit the physician to make a prompt, accurate diagnosis and thus prevent a significant amount of unnecessary hospitalization.

Kai Sturmann, MD
Timothy Shoen, MD
Department of Emergency Medicine
Allen W Filiberti, MD
Division of Cardiology
Worcester City Hospital
Worcester, Massachusetts

Airway Obstruction from Metastatic Melanoma

To the Editor:

A 36-year-old woman presented to the ED complaining of a persistent, nonproductive cough and exertional dyspnea. She stated that she had been treated by her family physician for "bronchitis" for the last two weeks with tetracycline 250 mg PO qid and an expectorant. An outpatient chest radiograph one week prior to presentation was negative. She began to have increased dyspnea and persistent coughing on the day of admission. Medical history was remarkable for a malignant melanoma of her left neck that had been widely excised in 1972. She had remained clinically asymptomatic, and yearly chest radiographs had been negative since that time. Review of systems was negative except for her chief complaint.

Physical examination revealed a woman in moderate distress secondary to dyspnea. Vital signs were as follows: blood pressure, 100/60 mm Hg; pulse, 84; respirations, 28; and temperature, 36.6 C. Physical examination was remarkable for inspiratory stridor that was audible on entering the examining room. The patient stated that she had noticed a "wheeze" for approximately one week prior to admission. Suprasternal retractions and difficulty with phonation also were present. There was no cyanosis or clubbing of the extremities. There was an 8-cm scar over the left sternocleidomastoid area. Scattered inspiratory and expiratory wheezes were heard over the right lung base. There was no cervical or peripheral adenopathy. The abdominal examination was negative for hepatosplenomegaly.

The patient was treated with an epiglottis protocol. A portable lateral neck radiograph was performed (Figure) in an examining room with laryngoscopes, endotracheal tube, and cricothyroidotomy instrumentation that was readily available. The radiograph revealed a mass lesion arising from the anterior wall of the trachea in the subglottic area, producing considerable encroachment on the tracheal lumen. Due to the nature and level of the obstruction, preparations were made for tracheostomy. The patient's condition did not deteriorate, and it was believed that the procedure would best be done in the operating room.

The patient was taken to the operating room where, under general anesthesia, a tracheostomy was performed through the second and third tracheal rings with removal of a large pigmented tumor. The patient tolerated the procedure well. Histologic examination of the tumor revealed metastatic melanoma.

Upper airway obstruction is a medical emergency. The most common causes are infection, foreign body aspiration, trauma, anaphylaxis, and hemorrhage.[1] This case represents a rare form of airway obstruction.

Tumor is an uncommon cause of upper airway obstruction. Tumors arising in the hypopharynx seldom have airway obstruction as a significant symptom. Malignant obstruction of the trachea is even more unusual because of the low frequency of primary and metastatic lesions. The trachea apparently is resistant to invasion by adjacent malignancies.[2] Primary tracheal malignancies are exceedingly rare, with squamous cell being the most common.[3]

Secondary tumors are most likely to affect the upper trachea by encroachment or invasion by the primary tumor or its metastases.[2] These tumors include lung, esophageal, and thyroid carcinoma. Freeland[4] and colleagues reported four cases of metastases to the larynx from distant primaries, including ovarian cystadenoma, melanoma, nasopharyngeal carcinoma, and myeloblastic leukemia.

The earliest symptom of upper airway obstruction secondary to tumor is exertional dyspnea. Exertional dyspnea does not occur until the tracheal lumen is less than 6 mm.[5] Our patient's lumen was 2 mm at presentation. Wheezing, inspiratory stridor, and orthopnea appear with progressive narrowing of the lumen. Cough is common. One can see that in a seemingly healthy individual these symptoms might be mistaken for an upper or lower respiratory infection. Hemoptysis is variable. Upper airway obstruction from tumor encroachment usually is gradual in onset because patients accommodate. Sudden decompensation is uncommon, but can occur.[2]

Evaluation should begin with soft tissue radiographs. A lateral neck radiograph will best delineate the upper third of the trachea. Swallowing views will bring more tracheal shadows out of the chest and into view. Bilateral oblique views through the chest give full-length tracheal contours.[2]

Treatment is directed toward maintaining a patent airway. If possible, one should ascertain the level of obstruction before attempting tracheal intubation, cricothyroidotomy, or tracheostomy.[6] In our case, tracheostomy was the appropriate method of airway control because of the nature of the obstruction.

Jay S. Feldstein, DO
James S. Bouzoukis, MD
Department of Emergency Medicine
Wilmington Medical Center
Wilmington, Delaware

1. Boster RB, Martinez SA: Acute upper airway obstruction in the adult. *Postgrad Med* 1982;72:50-67.

2. Sise JG, Crichlow RW: *Semin Oncol* 1978;5:213-223.

3. Batsakis J: *Tumors of the Head and Neck*. Baltimore, Williams and Wilkins, 1979, p 91.

4. Freeland AP, van Nostrand AWP, Jahn AF, et al: Metastases to the larynx. *J Otolaryngol* 1979;5:448-456.

5. Miller RD, Hyatt RE: Obstructing lesions of the larynx and trachea. *Mayo Clin Proc* 1969;44:145-161.

6. Hanline MH Jr: Tracheotomy in upper airway obstruction (letter). *South Med J* 1981;74:899.

BOOK REVIEWS

Pain, Analgesia, and Addiction

B Stimmel
1983. Raven Press. 326 pages. $45 (cloth)

Most emergency physicians, in the course of daily dealings with pain, undoubtedly have developed somewhat mechanistic views of pain and its treatment. The same probably is true of the treatment of analgesic overdoses and withdrawal states. It is refreshing, if one has the time and specific interest, to review in some depth those pharmacologic agents most frequently used for pain control.

In addition to refreshing the reader on pharmacologic principles of analgesia, *Pain, Analgesia, and Addiction* attempts to shed light on a number of aspects of the chemical control of pain, such as alternative and adjunctive medications, addiction states, withdrawal syndromes, and pain management in the elderly. The section on iatrogenic drug dependence, with a discussion of the impaired physician, is highly recommended. The book is well organized and very readable, with excellent tables and diagrams, particularly in the neuroanatomy and pharmacology sections.

The text falters for the emergency physician in several areas. It is surprising, for instance, that there is no mention of the use of local anesthetic agents (except cocaine), nitrous oxide, or other inhalants. In addition the author routinely discusses the management of toxicity of analgesic agents, but his management recommendations are usually brief and occasionally lack state-of-the-art precision.

This book can be heartily recommended as an excellent review of pain and its control, but it probably will be of limited value as a quick reference in the emergency department.

Donald B Kunkel, MD
Department of Medical Toxicology
St Luke's Hospital
Phoenix, Arizona

John H van de Leuv, MD, CM — Editor
Indianapolis, Indiana

Diagnosis and Treatment of Mushroom Poisoning

C Scates, BH Rumack
Post Falls, Idaho (chart)
Kit Scates Myco Charts

"Diagnosis and Treatment of Mushroom Poisoning" is a color wall chart produced by Catherine Scates of the North American Mycological Association, with the cooperation and approval of Barry H Rumack, MD, director of the Rocky Mountain Poison Center. Dr Rumack is the primary medical source today on the management of mushroom poisoning.

The chart is well organized and provides an amazing amount of information. Superb color photographs aid in mushroom identification. Information provided includes onset of symptoms, class and toxins, clinical signs and symptoms, organs involved, and suggested treatment. There is also a section on mushroom terminology.

The "suggested treatment" section discusses the major treatment modalities that should be considered for each poisoning group. The language is diplomatic, allowing room for individual clinical judgment.

A major problem in mushroom poisoning is mushroom identification — physicians often are dealing with an unknown and are left with general supportive care as the only approach to treatment. This chart can aid in proper identification of mushrooms.

It may be helpful to list geographical locations on subsequent printings of the chart. Orellanine, the "eighth" group of mushrooms, has been included in this chart. The delayed symptomatology and nephrotoxicity of *cortinarius orellanus* and other species has been reported only in Europe. While *cortinarius gertilis* is found on the Pacific Coast, no toxic cases have been reported in the United States. The chart may be ordered from Kit Scates Myco-Charts, E 2830 Marine Drive, Post Falls, Idaho 83854.

The price of the chart is $24.95 each for hospitals plus $2 for postage and handling. A 20% discount is offered to members of medical societies and mycological societies for individual copies.

This is an excellent chart, authoritative and useful to the emergency physician, which is highly recommended for every emergency department in the United States.

Lester M Haddad, MD
Clinical Assistant Professor
National Capital Poison Center
Department of Emergency Medicine
Georgetown University Hospital
Washington, DC

Prehospital Emergency Pharmacology

BE Bledsoe, G Bosker, FJ Papa
1984. Robert J Brady Company. $16.95 (soft cover)

Prehospital Emergency Pharmacology is of value to emergency medicine practitioners, students, and emergency medical services (EMS) personnel. It is a comprehensive and exceptionally complete guide to prehospital emergency pharmacology. It begins with fundamental background information with which prehospital professionals must be familiar. The section on terminology and abbreviations, previously an area in which substantial information was difficult to locate, is a rewarding addition to the text.

The section addressing drug administration is covered with simplicity and excellent detail. Consequently this subject is easier for the reader to understand and utilize for

review purposes. Excellent reinforcement is afforded drug dosage and calculations. Although brief it utilizes pertinent situations and problems familiar to prehospital professionals.

The drugs and their usage are presented in appropriate format, allowing easy access for the reader. Included are descriptions, indications, contraindications, precautions, dosage, route, and how supplied. Consequently the difficult task of paramedic training of this subject is made easier and more understandable.

Another refreshing discovery is a quick reference guide to commonly used emergency medications that addresses most phases of EMS; a pediatric conversion table is included.

Recommendation for usage of this text are numerous. EMS personnel would benefit by using this text in the classroom, in clinical areas, and in the field. Emergency physicians, emergency department nurses, and critical care staff should consider this text for use as a review guide and as teaching support material when instructing EMS personnel.

Where it is necessary for EMS personnel to use prehospital emergency drugs in a critical setting, a text of this caliber is recommended. It offers a quick reference for immediate use or for review purposes.

Robert D Aranosian, DO, Director
Emergency Medicine/Medical Affairs
Community Memorial Hospital
Cheboygan, Michigan

Drug-Induced Ocular Side Effects and Drug Interactions, ed 2

FT Fraunfelder, SM Meyer (eds)
1982 Lea & Febiger 544 pages. $30 (hardbound)

The second edition of this reference work follows a format that proved successful in the first edition. The editors carefully introduce the format used in each of the chapters, which includes drug class, generic and common proprietary names, indications for use of the drug, ocular side effects, the significance or importance of the side effect in ophthalmology, a list of common drug interactions, and pertinent references.

As reflected in a useful table of contents, the chapters in the text are defined according to 13 categories of drug use: antiinfectives, gastrointestinal agents, homeostatic and nutrient agents, oncolytic agents, and the like. In addition the text contains two indices. The "Index of Side Effects" catalogues signs and symptoms in ophthalmology from "abnormal conjugate deviations," "blepharospasm," and "cataracts" to toxic amblyopia, uveitis, and visual hallucinations. The second index refers to drugs discussed in the text. Generic names, many proprietary names, and drug classes are included.

The sections in each chapter are allocated by class of drug. These deal with drug interactions, but do not detail additional ocular side effects that result from additive or synergistic drug combinations. Rather the editors have selected a simple classification of increased, decreased, or variable effect of one drug on the action of others that may be used in ophthalmology.

The scope of agents presented by the editors is comprehensive. The references for each section are selective but highly relevant, and they provide an easy access to the medical literature pertinent to a class of agents.

The book is clearly dedicated to the ophthalmologist as a reference source. In toxicology eye findings usually are quite variable, and it is unlikely that this text would assist in the diagnosis of the drug-intoxicated patient. For those cases in which the eye findings are the basis of the chief complaint or the only prominent feature of the clinical problem in the emergency department, however, this reference would be very useful.

Robert G Peterson, MD, PhD
Associate Professor of Pediatrics and Pharmacology
University of Ottawa
Medical Director
Poison Information Center
Children's Hospital of Eastern Ontario

PLACEMENT

Physician Available

ABEM CERTIFIED: Age 37, residing in Palm Beach County, seeking full- or part-time position in the area. Six years experience as director in a 250-bed hospital. Well versed in administration, teaching, quality assurance, marketing. Respond to ACEP Box 930, PO Box 619911, Dallas, TX 75261-9911.

DIPLOMATE ABEM: FACEP, age 35. Experienced emergency department director, ATLS, ACLS instructor/trainer. Seeking partnership position in challenging ED. We will consider above-average offers. Reply ACEP Box 924, PO Box 619911, Dallas, TX 75261-9911.

DIPLOMATE ABEM AND ABFP: FACEP, instructor in ACLS, ATLS, and PALS. Special interests in EMS and psychiatry. Teaching and administrative experience. Looking for director or staff position within 1 hours of New York City. ACEP Box 907, PO Box 619911, Dallas, TX 75261-9911.

FACEP: Age 39. Current director. Excellent communicative, marketing, and problem-solving abilities. Experience training EM residents, nurses, and paramedics. Prefer assistant director, director, or partner in Illinois or Northeast, but will consider all above average offers in strict confidence. Reply to ACEP Box 915, PO Box 619911, Dallas, TX 75261-9911.

NEW DIRECTIONS: Experienced group of 13 ED physicians looking for unique practice opportunities. Individual MDs available for 1-3 months, possibly longer. Dull and humdrum need not reply. ACEP Box 737, PO Box 619911, Dallas, TX, 75261-9911.

Position Available

ACADEMIC EMERGENCY MEDICINE: Faculty positions available in the Section of Emergency Medicine at the University of Arizona. Responsibilities include clinical, administrative, and teaching activities. Applicants should be board certified/prepared in emergency medicine. Please contact Harvey W. Meislin, MD, Section of Emergency Medicine, 1501 N Campbell Ave, Tucson, AZ 85724. The University of Arizona is an Affirmative Action/Equal Opportunity Employer.

ACADEMIC EMERGENCY MEDICINE: Full-time academic positions available immediately in three-year-old emergency medicine residency program to meet expanding needs in area of resident supervision, EMS direction, development of research program and administration. Level I trauma center with affiliated county hospital with 37,000 annual visits. Emergency medicine training or appropriate training with ABEM diplomacy required. Excellent remuneration and fringes together with beautiful Southwestern climate. For details contact V Gail Ray, MD, Texas Tech University, RAHC, Dept of Surgery, Division of Trauma and Emergency Medicine, 4800 Alberta Ave, El Paso, TX 79905, phone 915 533-3020, ext 386.

ACADEMIC EMERGENCY MEDICINE: University emergency medicine residency program director position available. Emergency medicine residency-trained and ABEM-certified applicants only. Wayne State University, Detroit Receiving Hospital. Full-time academic appointment. Generous compensation with full benefits and 20 vacation days per year. Send CV to Brooks F. Bock, MD, Chief, Emergency Medicine, Detroit Receiving Hospital, 4201 St Antoine, Detroit, MI 48201.

ACADEMIC EMERGENCY PHYSICIAN: Ideal practice setting in private suburban-type Level I trauma center with 7 residency training programs and university affiliation seeks board-certified -prepared physician. Compensation approximately 90K based on CV. ACLS and ATLS instructor preferred. Send CV to Mike Weaver, MD, 4505 Headwood #1, Kansas City, MO 64111, or call 816/931-8881.

ALABAMA: Emergency physicians needed for 377-bed hospital located in large city, 26,000 annual ED visits. Access to major university. Excellent compensation with malpractice insurance provided. Independent contractor status. For further information contact Chris Gaffney, Coastal Emergency Services, Inc, 1900 Century Pl, Ste 340, Atlanta, GA 30345, 404 325-1645 in GA, 800 241-7471.

ALABAMA: Immediate two full-time positions available in freestanding ambulatory care clinic located in a good community with equity position. Remuneration first year $70-80,000 with real possibility to double within one to two years. Send CV to Physicians, Route 1, Box 46, Pike Road, Alabama 36064, or call Rusti at 205 271-4410.

ALABAMA: Physician wanted. Compensation guarantee and fee for service. Contact Florence Emergency Physicians, Dr Joseph Yates, Director, 114 W Doctor Hicks Blvd, Ste 400, Florence, AL 35630, 205 767-4591 or 205 766-7739 (home).

ALABAMA: Well-established, dynamic group staffing emergency departments in Alabama. Salary $72,000 to $85,000. Growth potential with management opportunities. Contact The Emergency Group, PO Box 817, Enterprise, AL, 205 347-3682.

ALASKA: Physicians needed immediately to join established group staffing urgent care facilities in Anchorage. Guaranteed hourly rate plus profitsharing incentives and paid malpractice insurance. Primary care training or experience required. Please send replies to Scott P Mackie, MD, FACEP, PO Box 111767, Anchorage, AK 99511-1767.

ARIZONA: Positions available in emergency medicine in the Phoenix Mesa metropolitan area. Excellent group of colleagues and active practice. Send curriculum vitae to Richard A Melde, MD, Arizona Emergency Physicians, Ltd, Desert Samaritan Hospital, 1400 S Dobson Rd, Mesa, AZ 85202, or call Ms Nancy Hayward at 602 833-6180.

ARIZONA, Phoenix: Expanding physician-owned emergency group accepting applications for full-time, career-oriented emergency physicians. Flexible work schedules, excellent benefit package, ideal working and living conditions. Send CV to Emergency Physicians, Inc, 1741 E. Morten Ave, Ste B, Phoenix, AZ 85020, or call Thomas C Patterson, MD, or Paul Wheeler at 602 870-0194.

ARIZONA, Phoenix: Maricopa Medical Center, a 400 bed county teaching hospital, is seeking residency trained emergency physicians to join a full time eleven-member group in recently established Department of Emergency Medicine. MMC sees 50,000 ED patients annually and is a Level I trauma center and paramedic base station. Physicians are active in ACLS, ATLS, and paramedic teaching. Salary is competitive and malpractice is provided. Contact Richard Walsh, MD, Chairman, Department of Emergency Medicine, Maricopa Medical Center, PO Box 5099, Phoenix, AZ 85010.

CALIFORNIA: Board certified/qualified or residency trained emergency physicians wanted to join 320 physician multispecialty group. Competitive salary and excellent fringe benefits. Newly remodeled Sierra Sierra and Sun Lakes area. Outstanding schools required. Send curriculum vitae to Mr. Gary E. White, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865. An Equal Opportunity Employer.

CALIFORNIA: [illegible]

sibilities in a stable, established group with partnership advancement opportunity. Contact California Emergency Physicians, 440 Grand Ave, Suite 500, Oakland, CA 94610; 415/832-6400.

CALIFORNIA: Join a partnership of established physicians providing urgent and ambulatory care in both northern and southern California. Physicians earn a guaranteed minimum with strong incentive package and have the opportunity to quickly become partners. Our attractive centers are rapidly growing. Please indicate your geographic preference (LA or San Francisco Bay area) and contact California Emergency Physicians, 440 Grand Ave, Ste 500, Oakland, CA 94610; 415/832-6400.

CALIFORNIA, Partnerships: Available with a seasoned group in a joint venture mode to establish freestanding ambulatory care center. Excellent site, physician oriented, financing aid available. Send CV to National Medical Centers, 866 Plumas St, Ste B, Yuba City, CA 95991-4016.

CALIFORNIA: People-oriented physician sought to join group of like physicians operating a small series of freestanding clinics in northern California. Camaraderie, recreational opportunities and the possibility of an early management or equity partnership role are all part of the package. Send CV to ACEP Box 668, PO Box 619911, Dallas, TX 75261-9911.

CALIFORNIA: The County of Los Angeles and the UCLA School of Medicine are seeking applicants for the position of Director of Emergency Services at the Los Angeles County-Olive View Medical Center. Olive View Medical Center is an acute care hospital in the San Fernando Valley area of Los Angeles. The hospital facilities are new. There is an approved residency training program in emergency medicine, fully integrated with that of the UCLA Medical Center (Westwood). The desirable candidate will be a person board certified in emergency medicine or a person board prepared in emergency medicine with board certification in another specialty. Candidates should have a strong academic background with an interest in research, as well as experience in teaching and patient care. Qualified candidates send curriculum vitae and support materials to Marshall T Morgan, MD, Chairman of the Search Committee, Olive View Medical Center, Rm 404, S Tower Bldg, 7533 Van Nuys Blvd, Van Nuys, CA 91405. An Affirmative Action/Equal Opportunity Employer.

CALIFORNIA, Hemet: Opening for experienced emergency physician to join established group in moderate-volume ED. Board certified/prepared in EM preferred. Competitive salary with malpractice paid and opportunity for full partnership. Send CV to Hemet Emergency Medical Group, 27692 Soboba St, Hemet, CA 92344.

CALIFORNIA, Los Angeles: Openings for career-oriented emergency medicine specialists. Excellent compensation and career growth opportunities. Write Barry Staum, MD, Janzen, Johnston and Rockwell, 1520 Arizona Ave, Santa Monica, CA 90404; or call 213/451-0783.

CALIFORNIA, Northern: Our 45-man multispecialty group is adding full- and part-time physicians to the staff of our minor emergency centers in the San Francisco Bay area. Initial salary and benefit package leading to senior status with full economic participation. Board-prepared physicians with emergency care experience should contact Recruitment Director, San Jose Medical Group, 45 S 17th St, San Jose, CA 95112.

CALIFORNIA, Sacramento: Partnership opportunity with established multi-hospital group practicing in Northern California. Full-time positions available for board-prepared or board-certified emergency physicians. Competitive salary and benefits. Malpractice paid. All hospitals with moderate volumes, many act as EMS basestations. Send CV to Sacramento Emergency Medical Group, PO Box 214584, Sacramento, CA 95821.

CALIFORNIA, San Francisco: CVs being accepted for experienced, career-oriented emergency physician to join established ED group in medium-sized, full-service community hospital. Fee-for-service (with guaranteed minimum), malpractice insurance paid, flexible schedules. Send to Emergency Department, 1580 Valencia St, San Francisco, CA 94110.

CALIFORNIA, San Francisco Bay Area: Emergency physician, BC or BP, wanted for full-time overnight position at a Kaiser-Permanente Medical Center, large nationwide HMO. Spacious new facility with good specialty backup. 60,000 outpatient visits/yr, competitive salary, exceptional benefits, fine school system, many recreational and cultural opportunities. Send CV to Forrest J Cioppa, MD, Kaiser Foundation Hospital, 1425 S Main St, Walnut Creek, CA 94596; 415/943-2080.

CALIFORNIA, San Francisco Bay Area: Emergency physician group is accepting CVs from physicians board certified/prepared in emergency medicine. Also accepting CVs from qualified physicians interested in urgent care opportunities. Competitive hourly, paid malpractice, and opportunity to grow with small, high-quality group. Send CV to Chase Dennis Group, 873 Corcoran Ct, Benicia, CA 94510.

CALIFORNIA, San Joaquin Valley: Personable BC/BP emergency physician needed to associate with group of career emergency physicians in a progressive community non-profit hospital. Emergency department is full department status, about 32,000 visits/year. Paramedic base station, trauma receiving hospital. Excellent support from consulting staff in all specialties, including cardiac surgery. Interest in EMS desirable. Teaching position in emergency medicine residency available. Generous financial arrangements with parity at two (2) years. Send CV in complete confidence to PO Box 3893, Pinedale, CA 93650.

CALIFORNIA, San Jose: Emergency physician sought for position as part-time director of poison control center at a university-affiliated teaching hospital. Responsibilities include patient care in the emergency department. Must be board certified/prepared in clinical toxicology. Fee-for-service with minimum guarantee. Contact James B Lane, MD, 1625 The Alameda, #201, San Jose, CA 95126; 408/293-8881.

CALIFORNIA, San Jose: Position available for board-certified/-prepared emergency physician with established group practicing in San Francisco Bay area in a high-volume university-affiliated teaching hospital and a large community hospital with recently established trauma service. Fee-for-service compensation/minimum guaranteed. Contact James B Lane, MD, 1625 The Alameda, #201, San Jose, CA 95126, 408/293-8881.

CALIFORNIA, San Luis Obispo Area: Seeking experienced physician for progressive urgent care center. Benefits include liberal scheduling, malpractice, $75,000 per year guaranteed income, plus profitsharing plan. Send CV to Doctors' EmergiCenter, 900 Grand Ave, Arroyo Grande, CA 93420, 805/489-4357.

CALIFORNIA, Southern: Emergency physician needed for full-time position in the high desert area. Relocation from Southern California not required. $75,000 annual starting salary. Contact Dr Pettinger at 13238 Topsanna, Apple Valley, CA 92307, or call 619 247-2761 or 619 366-3711, ext 127.

CALIFORNIA, Southern: Multi-specialty group practice recruiting urgent care center director. Board certified/prepared. Excellent opportunity in desirable area of Southern California. Congenial staff, excellent working conditions, and fringe benefits. Salary negotiable. Submit CV to ACEP Box 920, PO Box 619911, Dallas, TX 75261-9911.

CALIFORNIA and FLORIDA: Emergency physician. Groups seeking additional physician in northern California Sierra community and St Petersburg, Florida. Board certified/prepared by experience or residency. Salary, incentives, and malpractice provided. Send CV to Marilyn Bahou, Manager, Physician Relations, National Medical Enterprises, PO Box 2140, Santa Monica, CA 90406.

CAREER-MINDED PHYSICIAN: Board-certified physician needed to complement experienced, existing physician staff serving in our new emergency department. The hospital is a large and expanding referral center handling 30,000 emergency cases per year. Position offers exceptional benefits and remuneration package, as well as ready access to Northern Michigan's recreational areas. For additional information send curriculum vitae or contact Mr Louis E Zeile, President, St Luke's Hospital, 705 Cooper, Saginaw, MI 48602; 517/771-6000.

COLORADO, Ft Collins: Position for full-time physician in a freestanding center. Excellent lifestyle available. Close to skiing and a broad array of outdoor sports. Family practice or emergency medicine. Excellent compensation. No nights. Send CV to IntraWest Medical Services, PC, PO Box 1649, Laramie, WY 82070; or call Sheldon Truax at 307/745-3169, Donald Cantway, MD, at 303/879-6020.

COLORADO, Ft Collins: Well-established urgent care clinic seeking full-time physician with demonstrated FP, EM, and interpersonal skills. Profitsharing; continuing care option. Outstanding opportunity in a university town of 80,000. Generalcare Clinic, 1045 Garfield, Ft Collins, CO 80524; 303/482-6620.

CONNECTICUT, Bridgeport Hospital: Departmental status ED seeks boarded or board-prepared career-oriented physicians to join the most stable emergency physician group in Connecticut. 600 beds, 52,000 ED visits annually, community teaching hospital with 80-member housestaff and Yale affiliation. Competitive salary, full fringe benefits with opportunity for partnership. H Lyle Stotts, MD, FACEP, Chairman, Bridgeport Hospital, 267 Grant St, Bridgeport, CT 06602.

CONNECTICUT: Primary care physicians, BC/BP, needed to join expanding walk-in medical center group in central Connecticut. Full- or part-time positions and medical directorships available. Compensation package includes competitive salary, malpractice insurance, and profitsharing opportunity. Stimulating work experience in a comfortable setting with flexible scheduling. Send CV to PhysicianCare, 28 Main St, East Hartford, CT 06118; or call 203/569-8644.

CONNECTICUT: 303-bed community hospital seeks emergency medicine-trained or practice tract-prepared physician to join our full-time staff of seven emergency physicians. Our newly renovated ED is a full hospital department with an active educational program (including ACLS) and an excellent paramedic program. An ambulatory care center is in the planning stages. Manchester, Connecticut, is a town of 50,000 near Hartford with a choice of living options from urban to rural in the immediate area. Outdoor sports, seashore, mountains, and cultural activities are available within a short drive. Send CV to Joel J Reich, MD, FACEP, Chairman, Emergency Department, Manchester Memorial Hospital, 71 Haynes St, Manchester, CT 06040.

DELAWARE: Board-prepared or board-certified emergency physician to join well-established group. Very active emergency practice. Approximately 38,000 visits per year. Excellent medical staff backup. Full department status. Hospital-based paramedic program. Competitive salary and benefits. One hour to Chesapeake Bay and Atlantic Ocean. Send CV to John C Sewell, MD, FACEP, 640 S State St, Dover, DE 19901; 302/734-0558.

DIRECTOR, Greenville, Mississippi: Delta city of 50,000 surrounded by lakes and recreational areas. Flexible schedules will accommodate vacations and hunting season. Income range of $80-100,000 depending on pathology and volume. Busy ED with high degree of trauma sees 18,500 patients per year and has shown steady growth since 1976. New 11,000 sq ft department in 250-bed medical center which serves as EMS satellite center to University of Mississippi. ED sees 98% of patients with excellent medical staff backup. This is a fee-for-service opportunity where income potential is not limited. Fischer Mangold provides most malpractice coverage. CME, potential group incentive after 3 years, and directorships with incentive base. Contact Ken Baker, Director of Physician Recruitment, Fischer Mangold Group, PO Box 788, Pleasanton, CA 94566; 800/227-2092; in California 415/484-1200.

EMERGENCY AND PRIMARY CARE PHYSICIAN: We are looking for a career-oriented physician to join our established and expanding group which includes two ambulatory care facilities and a family practice clinic. Full specialty backup, excellent salary and benefits, including pension plan and insurance in a family-oriented community. Please send curriculum vitae to First Medical, Inc, PO Drawer 3047, Hattiesburg, MS 39401.

EMERGENCY CONSULTANTS, INC: Has openings in Texas, Ohio, Illinois, Michigan, Wisconsin, Indiana, New York, Pennsylvania, Tennessee, Virginia, and West Virginia emergency departments. Independent contractor status with competitive compensation and paid malpractice insurance. Forward CV with availability date and geographic preference to Emergency Consultants, Inc, 2240 S Airport Rd, Traverse City, MI 49684; 800 253-1795; in Michigan 800 632-3496.

Emergency Department Physicians, Inc.

Emergency physician and urgent care center practice career opportunities with established group for highly competent individuals

+ Active Growth
+ Group health insurance
+ Comprehensive Continuing Education (ACLS, ATLS)
+ Vested group interest, stock ownership after 2 years

Florida
Georgia
Southern California
Stateline, NV at Lake Tahoe
Mississippi

Experience and/or residency training in acute care medical specialty preferred. Send resume to EDP, PO Box 9639, Marina Del Rey, CA 90295. For further information call or write:

Florida: Steve Watsky, MD, 707 40th Street West, Palmetto, FL 33561; (813) 746-5111

All others: Philip J Fagan, Jr, MD, 4640 Admiralty Way #305, Marina Del Rey, CA 90292; (213) 822-1312

EMERGENCY MEDICINE: Excellent opportunity for emergency physician in a 552-bed major teaching hospital in Philadelphia. A state-of-the-art facility. Emergency medicine residency program not required. All business considerations are negotiable. Contact Linda Hay, 800 441-0996; or in Pennsylvania 215/896-5080.

EMERGENCY MEDICINE CHAIRMAN AND STAFF: Daniel Stern and Associates represents a variety of hospitals, including community to large university trauma centers. We are seeking career emergency physicians for staff and directorship positions. Physicians can be prepared either through the practice route or EM residency training. Qualified candidates should inquire about positions paying $70,000 to $140,000 in several mid-Atlantic states. Please forward complete CV to Daniel Stern and Associates, The Medical Center East, 211 N Whitfield St, Pittsburgh, PA 15206. Inquire directly by calling 412/363-9700 in Pennsylvania; 800/438-2476 in US.

EMERGENCY MEDICINE PHYSICIANS: We are seeking BC/BP emergency medicine physicians who are personable and possess excellent clinical and communication skills to join an existing group of career emergency physicians. Positions available in Hawaii and the greater Kansas City metropolitan area. Annual compensation packages range from $63,000 to $120,000 and are related to patient volume. For additional information please send CV to Cecelia Cleary, Emergency Medical Services, 3212 Central Ave, Kansas City, MO 64111, or call 800/821-5147 or 816/561-1025.

EMERGENCY MEDICINE POSITION AVAILABLE: Opportunity for experienced emergency physician to join professional group practicing in Northwestern Indiana. Contact Dr Daniel Philipsborn at 312/248-5557.

EMERGENCY MEDICINE RESIDENCY-TRAINED GROUP: Seeks association with emergency residency-trained graduates to staff new hospitals in Ohio and South Carolina. Successful candidates to be immediate profit sharers. Guaranteed annual salary and profits of six figures per year. Early share holding in the corporation is anticipated. Send curriculum vitae to ACEP Box 722, PO Box 619911, Dallas, TX 75261-9911.

EMERGENCY PHYSICIAN: Mount Sinai Hospital, a 380-bed university affiliated community hospital with approximately 45,000 emergency visits year, seeks full-time emergency physician to join established group. Prefer candidate BC BP in emergency medicine, internal medicine, or surgical residency program completion. ACLS and ATLS certification necessary. Our progressive facility offers a highly comprehensive benefits package and competitive salary based on level of professional expertise. Submit CV or contact Dr M Ostroff, Chief, Emergency Medicine, Mount Sinai Hospital, 500 Blue Hills Avenue, Hartford, CT 06112, 203/242-4431. An Equal Opportunity Employer.

EMERGENCY PHYSICIAN: Sought for downtown medium-volume emergency department to complete group of five. Participation in medical command of ALS system serving county of 312,000. New well-designed emergency care unit in July of 1985. Stable city of 78,000 located on the Schuylkill River in the Allegheny foothills. Good access to Jersey Shore, Chesapeake Bay, Pocono Mountain resorts, Philadelphia, New York, and Baltimore. 42 hours a week plus on-call time; $100,000+ per year. Board certified/prepared or substantial experience considered; US trained only. Send CV to R Tempest Lowry, MD, Director, Department of Emergency Medicine, Community General Hospital, Reading, PA 19601; or call 215/378-8369.

EMERGENCY PHYSICIAN: University Hospital of Jacksonville, a major teaching affiliate hospital of the University of Florida, announces the availability of a position in the division of emergency medicine. MD required. Board preparation or certification required. Strong teaching, research publication interest required. Level I trauma center, large, active emergency medicine residency. Salary negotiable. Application deadline August 30, 1985. Starting date November 1, 1985 or before. Contact Terry L MacMath, MD, Search Committee Chairman, University Hospital of Jacksonville, 655 W 8th St, Jacksonville, FL 32209. Affirmative Action/Equal Opportunity Employer.

EMERGENCY PHYSICIANS: Sought for Department of Emergency Medicine, Rhode Island Hospital. Teaching and patient care in a Brown University Biology and Medicine affiliated major hospital. Must be board qualified, emergency medicine. Apply J Franaszek, MD, Emergency Medicine, Rhode Island Hospital, 593 Eddy St, Providence, RI 02902; 401/277-5826. AA/EOE.

EMERGENCY PHYSICIANS-BC/BP: To join expanding HMO hospital-based emergency services program. Salary $65,000-$90,000 depending on experience and administrative responsibilities. Excellent benefit package. Send CV to Jennifer Leaning, MD, Harvard Community Health Plan, One Fenway Plaza, Boston, MA 02215.

FLORIDA: Associate needed for very busy family and occupational practice located in southeastern Florida. Guaranteed minimum compensation plus substantial incentives and benefits. Excellent potential for equity position for the right individual. Considerable growth and expansion opportunity. Career-oriented physicians send resumes to Health Innovators, 8550 48th St, Ft Lauderdale, FL 33321.

FLORIDA: ED physician needed on Florida's southwest coast. Excellent opportunity to get in on the ground floor with a small independent group at a new hospital. Expected remuneration should exceed $100,000. Respond with CV to ACEP Box 929, PO Box 619911, Dallas, TX 75261-9911.

FLORIDA: Emergency medical group seeks qualified physicians to staff emergency departments and critical care units in the southeast Florida area. Board-certified -prepared physicians in emergency medicine, internal medicine, or family practice preferred. Competitive salary and benefits including paid malpractice insurance. Send CV to Emergency Medical Group, PA, 1400 NW 12th Ave, Miami, FL 33136, 305/325-1381.

FLORIDA: Emergency physician wanted to staff emergency depart-

COASTAL

A UNIQUE OPPORTUNITY OF CHOICE WITH LOCATIONS IN 15 STATES

Career practice, Part-time, Locum Tenens, Directorships, Teaching positions

REGIONAL OFFICES

Asheville	US 800-334-1630
	NC 704-253-1256
Atlanta	US 800-241-7471
	GA 404-325-1645
Augusta	GA 404-724-3368
Columbia	SC 803-782-7812
Columbus	OH 614-436-0418
	US 800-334-1630
Dallas	TX 214-258-5038
Durham	US 800-334-3306
	NC 800-672-1665
Ft. Lauderdale	US 800-328-1038
	FL 800-432-3093
Memphis	TN 901-767-1301
Richmond	US 800-551-1013
	VA 800-552-6638
Washington	VA 703-841-0333

COASTAL EMERGENCY SERVICES, INC.

ment and/or walk-in clinic on Florida's Gulf Coast. Great recreational opportunities. Excellent reimbursement. $90,000 yearly with growth potential. Three years practice experience versus residency required. Send CV to Dr. Wellington Chen, Ste 221, Box 1900, Sarasota, FL 33578. 813/349-0268.

FLORIDA: Established group has full-time opportunities for career-minded emergency physicians. Choose from various locations throughout Florida. Attractive remuneration and malpractice insurance provided. Please send CV to Karen Block, EMSA, 8200 W Sunrise Blvd, Bldg C, Plantation, FL 33322, or call 305/472-6922.

FLORIDA: Immediate full-time, part-time, and locum tenens emergency medicine opportunities in central, southeast, and Panhandle areas. Excellent growth potential with directorships available. Independent contractor status, flexible schedules and professional liability insurance provided. Contact Kathy Valli, Coastal Emergency Services, Inc, 2200 Commercial Blvd, Ste 203, Fort Lauderdale, FL 33309. 800/328-1038 in US, 800/432-3093 in FL.

FLORIDA: Independent emergency physician group seeks well-qualified applicants for full-time teaching/clinical duties in active university emergency care center. Full benefits package. Send CV to TEAM, PO Box 18091, Tampa, FL 33679.

FLORIDA: Need full-time or part-time physicians primarily for FEC, possibly for ED, in this beautiful west coast Florida area. Prefer career-oriented EM/FP, US-trained, board-certified/-prepared physicians with ACLS certification. Financial package very competitive with incentive bonus included. Florida license required. Contact South Florida Physicians, Inc, William Bess, MD, 1231 Hanton Ave, Ft Myers, FL 33901. 813/334-0611.

FLORIDA: Once in a lifetime opportunity in Florida Gulf Coast Sarasota area. Modern, fully-equipped 3,000 square foot clinic 50 yards from magnificent beach, very busy family practice $300,000 annual. For sale and/or seeking qualified associate. Write Oscar Klein, MD, 401 Manatee Ave W, Holmes Beach, FL 33510.

FLORIDA, Primary Care Centers: Recruiting aggressive emergency medicine and family practice trained physicians to staff centers on a full-time basis. Positions available in central and south Florida coastal communities. Excellent opportunity. Guaranteed salary, fee-for-service incentives, profit sharing with public corporation, malpractice insurance paid. Send CV to FMC, 250 N Babcock St, Ste 202, Melbourne, FL 32935.

FLORIDA: Young emergency physicians needed to join dynamic corporation of career-oriented emergency department professionals. EMS and ACLS involvement preferred. Several locations throughout the state, compatible with your choice and style of living. Florida license required and US trained. Contact David S Mitchell, Administrator, PO Box 6230, Clearwater, FL 33518, or call collect 813/446-7123.

FLORIDA: Young group of emergency specialists expanding ED coverage requires five positions, preferably residency trained or board prepared with ACLS certification. Salary very competitive with eventual partnership available. Write R Brereton, MD, 2030 SE 28th St, Cape Coral, FL 33904, or call 813/574-3442 or 813/334-5334.

FLORIDA, Central: Family physician or emergency physician needed for private freestanding emergency center in rapidly growing area. Excellent compensation. Please contact Martin W Cunningham, MD, 5030 SE 14th Pl, Ocala, FL 32671.

FLORIDA, Central: FEC operating as a medical center in rural area near Orlando providing acute medical care on a walk-in basis in addition to more traditional family practice care. Seeking FP-oriented physician. Directorship available. CME and malpractice provided. Competitive hourly rate. Write JM Garner, MD, Dept A, 890 SR 434 North, Altamonte Springs, FL 32714, or call Sandy Teal 305/788-0786.

FLORIDA, Central: Two full-time emergency physicians needed for hospital-based group. Time split between ED and walk-in clinic operations. Full specialty backup; malpractice paid. Florida license required; board certified/prepared in emergency medicine. 40,000+ patient visits per year. Partnership opportunities are available, salary more than competitive. Respond in confidence to ACEP Box 926, PO Box 619911, Dallas, TX 75261-9911.

FLORIDA, East Coast: Full-time emergency physician (2). Prefer US graduate, board certified prepared in emergency medical or primary care (family practice) or (internal medicine). 200-bed hospital with 12,000 ED visits per year. Good salary plus malpractice, health policy, disability policy, and term life insurance included. Excellent recreational area. Florida license required. Send replies and CV to Donald C Johnson, MD, 233 Osceola Ave, Ormond Beach, FL 32074, or call 904/672-4791.

FLORIDA, Ft Lauderdale: Emergency medicine group seeking career-oriented primary care emergency physician. Board certified/prepared in emergency medicine required. Full- or part-time. Submit CV to Barbara Fountain, 2727 E Oakland Park Blvd, Ft Lauderdale, FL 33306.

FLORIDA, Gainesville: Emergency physician needed for full-time position in busy community hospital emergency department. Excellent compensation in a university city. Prefer board certified/prepared in emergency medicine. Reply with CV to Jack Derovanesian, MD, Department of Emergency Medical Services, Alachua General Hospital, 801 SW 2nd Ave, Gainesville, FL 32602, 904/372-4321, ext 4135.

FLORIDA, Gulf Coast: Tampa to Naples. Board-certified or soon-to-be MDs to staff Walk-In Medical Centers. Ideal locations. Excellent remuneration. Send CV to Box 537, Venice, FL 33595, or call Raymond J McDermott, MD, FACEP, 813/485-4858 or 484-3453 after 6 pm.

FLORIDA, Jacksonville and St Augustine Areas: Young group of emergency physicians interested in expanding with residency-trained or highly experienced emergency physicians. Baseline board preparation required. Please contact Emergency Physicians, Inc, PO Box 5178, Jacksonville, FL 32207, 904/396-5682.

FLORIDA KEYS: Physician-owned group seeks career-oriented, experienced emergency physician, US trained, for low volume EDs and FEC from Key Largo to Key West. ACLS and ATLS required. Send CV and date available to Professional Emergency Services, Inc, PO Box 1131, Islamorada, FL 33036.

FLORIDA KEYS: Progressive physician-owned medical group has emergency department positions available. Experience in emergency medicine, board certified/prepared in emergency medicine or internal

medicine preferred. Competitive salary, fringe benefits, paid malpractice insurance. Send CV to Emergency Medical Group, PA, 1400 NW 12 Ave, Miami, FL 33136; or call 305/325-1381.

FLORIDA, Okeechobee: Emergency physician needed to work in a low-volume hospital near Lake Okeechobee. This rural area boasts great fishing and hunting. Excellent malpractice insurance provided. Please send CV to Harriet Schwartz, EMSA, 8200 W Sunrise Blvd, Bldg C, Plantation, FL 33322; or call 305/472-6922.

FLORIDA, Orlando: Young emergency group with immediate openings for full-time emergency physician in ED and emergency clinic; US training and ACLS required, excellent opportunity in community hospital. Send CV/inquiries to Jock Sneddon, MD, 6001 Vineland Rd, Ste 108, Orlando, FL 32819; 305/351-6682.

FLORIDA, Palm Beach County: New group staffing two beautiful hospitals seeks board-certified/-prepared ACLS emergency physicians. Excellent compensation and possibilities for advancement within the group. Malpractice and other benefits paid. Work ten shifts/month and enjoy this great area the other twenty. No administrative headaches. Individuals must have good people skills and experience in emergency medicine. Submit CV with references to Medical Director, PO Box 273503, Boca Raton, FL 33427.

FLORIDA, Panama City Beach: Associate director for moderate volume walk-in clinic in beautiful resort community. Prefer US-trained board-prepared MD or DO with family practice, emergency, or internal medicine experience. Guarantee $75,000 minimum plus percentage of gross and buy-in after six month tenure. Bay Walk-In Clinic, 2306 Highway 77, Panama City, FL 32406.

FLORIDA, Pensacola: Great opportunity for US-trained, experienced physician board certified/prepared in emergency or primary care medicine. For details contact John Hybart, MD, Emergency Dept, 5151 N 9th Ave, Pensacola, FL 32504; 904/474-7843.

FLORIDA, Sanibel/Ft Myers Beach: Now seeking several full-time physicians for our two freestanding emergency centers in this Gulf Coast resort area. Interested parties should send CV/inquiries to FEP, Inc, 1349 Chalon Lane, Ft Myers, FL 33907; or phone Dr Gavin at 813/482-8528 or 334-5334.

FLORIDA, Southeast Coastal Area: Unique opportunity for someone with internal medicine and emergency medicine experience. Expanding office based practice opportunity to earn $80,000 plus with equity participation available. Send CV in confidence to SRM & Associates, Inc, 1060 NE 28 Terrace, Pompano Beach, FL 33062.

FLORIDA, Tallahassee: Experienced emergency or family practice physician needed immediately for established walk-in clinic. Minimum guarantee with incentive bonus and partnership opportunity. Picturesque state capitol with excellent educational and cultural opportunities. Contact Jay Maggiore, MD, 904/234-8492.

EMP

EMERGENCY MEDICAL PHYSICIANS, P.C.

EMP is an expanding physician owned emergency group dedicated to excellence in patient care. Locations in Wyoming, South Dakota, and Washington. If you have residency training and/or experience and wish the challenge of participating in a congenial quality group, send CV or contact us at P.O. Box 805, Cheyenne, WY 82003, or 307/632-1436.

Don't take a chance with your career . . .

Emergency Physician Associates is seeking physicians with Emergency Medicine, Internal Medicine and Family Practice backgrounds who are experienced and interested in a challenging career in Emergency Medicine.

We are currently interviewing for positions in N.J., Pa., N.Y., De. and Md.

Send your C.V. in confidence to:
James E. George, M.D.
Emergency Physician Associates
P.O. Box 298
Woodbury, N.J. 08096
Or call Donna L. Wallace, Physician Recruitment at (609) 848-2088.

FLORIDA, Tampa, Clearwater, St Pete: Join the growth of a dynamic immediate care service network. Salary/early partnership options. US-trained, board-certified/-prepared, or experienced primary care physician, Florida license, good communications, excellent bedside manner essential. Send CV to D Duncan, 804 Franklin St Mall, Tampa, FL 33602; or call 813/229-0946.

GEORGIA: Emergency physician position available with well-established and respected group, mid-state area. Emergency medicine or family practice experience preferred. Income $110,000 plus. Send CV with references to John R Vaughn, MD, PO Box 77188, Atlanta, GA 30357; or call 912/922-0042.

GEORGIA, Swainsboro: Director needed for 73-bed hospital with an annual patient volume of 5,000 located in central Georgia. Short distance from Macon, Savannah, and Augusta, and 90 miles from the coast. Golfing and wildlife hunting are readily available. Independent contractor status with competitive compensation and malpractice provided. For further information contact Coastal Emergency Services, Inc, PO Box 925, Augusta, GA 30903; or call collect 404/724-3368.

HAWAII: Multi-hospital group has an opening for a full-time experienced emergency physician. Recent experience or residency required. Send resume to Mr Stephen Goodhart, Business Manager, Hawaii Emergency Physicians Associated, Inc, PO Box 1266, Kailua, HI 96734, 808 261-3326.

IDAHO: Eight-man group seeking ninth physician. Live near skiing, fishing, hunting, and wilderness while practicing in two modern medical centers, one is a trauma center with active EMS system. Seeking experienced EM physician preferably with administrative experience and EM certification. Competitive salary, malpractice, retirement, and other fringes. Send CV to PO Box 2572, Boise, ID 83701, or call 208/322-1730.

ILLINOIS: Emergency physicians needed by stable fee-for-service group located in central Illinois town of 40,000. Candidate should be board certified prepared in emergency medicine, family practice, or internal medicine. Salary $95,000 plus paid malpractice insurance. Early partnership. 18,000 annual visits. Paramedic program. Send CV to ACEP Box 922, PO Box 619911, Dallas, TX 75261-9911.

ILLINOIS: Private fee-for-service group staffing 400-bed community hospital seeks career-minded emergency physician to complete group. Active paramedic program and family practice residency program. Pleasant community of 90,000 centrally located with easy access to Chicago, St Louis, Indianapolis, and Big 10 campus. Good schools, parks, and recreation with active cultural groups. Physician-owned corporation provides life, medical, and disability insurance, pension and profitsharing plans. Income in excess of $90,000. Send resume to GA Snyder, MD, 1800 E Lake Shore Dr, Decatur, IL 62521.

ILLINOIS: Small Chicagoland group of emergency medicine specialists is seeking board-certified -prepared or residency-trained physician. New state-of-the-art trauma center EMS resource hospital, moderate volume, comfortable pace. Excellent compensation, guaranteed salary and incentives, flexible scheduling, pleasant community with liberal lifestyle. Individuals interested in ED administration and the development of new ED contracts are strongly encouraged to apply. Call Joe Danna, MD, Ron Kurzejka, MD at 815 937-2239 or 815 937-2100, St Mary's Hospital, Kankakee, IL.

ILLINOIS, Champaign/Urbana: Full- or part-time positions available for career emergency physicians, flexible scheduling with opportunity to work in hospital emergency department or FEC. Big 10 university town with state-of-the-art paramedic program. Send CV to Mercy Hospital, 1400 W Park, Urbana, IL 61801. Contact G Roth, MD, FACEP, 217 337-2131.

ILLINOIS, Chicago: Emergency department corporation needs full-time emergency physicians. ABEM-certified or prepared to sit for certification, to staff three 500-bed community hospitals in metropolitan Chicago. Good specialty backup. Administrative positions open to qualified applicants. Excellent salary, benefits. Send resume to EMSCO Ltd, 999 E Touhy Ave, Suite 145, Des Plaines, IL 60018, 312 297-5620.

ILLINOIS, Chicago: Immediate opening available for full-time emergency physician in community hospital, North Shore suburb of Chicago. Excellent compensation package including paid malpractice insurance. Satellite, intermediate care/sports medicine and wellness clinics to include staffing for fall 1985. Qualified candidates should send resume to Craig Dean, MD, Medical Center of Lake County, 900 Garfield, Libertyville, IL 60048.

ILLINOIS, Chicagoland: Established FFS corporation seeking board-certified -prepared emergency physicians for community hospitals in Chicago and suburbs. Directorship available to qualified candidate. Highly developed EMS program. Send CV to Emergency Physicians Group, 430 Milwaukee Ave, Prairie View, IL 60069. Contact Ms Barbara La Piana 312 634-4640.

CHICAGOLAND AREA: Immediate opportunities for emergency physicians who possess excellent clinical and communication skills to join longstanding group of emergency physicians. Positions available in Chicago, northwest suburbs, far northern suburbs bordering Wisconsin, and popular Wisconsin area bordering Illinois. If interested, send resume to Barbara Wiczynski, Medical Emergency Service Associates (MESA), SC, 15 S McHenry Rd, Ste 2, Buffalo Grove, IL 60090; or call collect 312 459-7304.

ILLINOIS, Galesburg: Full-time and part-time positions available for emergency physicians. Excellent compensation. 200-bed hospital, 10,000 annual visits. Immediate positions available. Contact Prakash N Khot, MD, 300 N Main, Abingdon, IL 61410, 309 342-7678, or 309 462-5626.

ILLINOIS, Joliet: Full time positions available for career emergency physicians committed to quality care and departmental-community development. Work with paramedic system, medical staff development, continuing medical education, planning of new ED and primary care locations in the community. Resource hospital with full specialty backup. Contact Brent Scott, MD, 187 Briarwood Central, Oak Brook, IL 60521, 312 986-5475 or 815 729-7563.

ILLINOIS, Peoria: 275 bed progressive community hospital centrally located between Chicago and St Louis is seeking an emergency physician. Board certification in emergency medicine preferred. Also considered are certifications in family medicine, internal medicine, or surgery. Sole contract status. Position available October, 1985. Flexible scheduling, malpractice insurance, competitive compensation. Excellent facilities and nursing staff, full specialty backup, moderate volume. Send curriculum vitae to R Garrett McGowan, Sr Vice President, Proctor Community Hospital, 5409 N Knoxville, Peoria, IL 61614, 309 691-4702.

ILLINOIS, Quad-Cities Area: Seeking emergency physicians with residency training and/or prior ED experience for both full-time and locum tenens opportunities in very attractive, moderate-volume facility. Excellent nursing staff. Directorship also available. Competitive hourly rates, malpractice insurance, and flexible scheduling. For more information, contact Emergency Consultants, Inc, 2240 S Airport Rd, Ste 101, Traverse City, MI 49684; 800/253-1795; or in MI 800/632-3496.

INDIANA, Emergency Medicine Position Available: Opportunity for experienced emergency physician to join professional group practicing in Hobart and Gary, Indiana. Contact Dr Cornelius Arnold at 312 747-7115.

INDIANA, Central: Physician-owned emergency group accepting applications for full-time career-oriented emergency physicians. Flexible work schedules and excellent benefit package. Part-time and directorship positions also available. Send CV to Margi Beeson, Midwest Medical Management, Inc, 528 Turtle Creek, North Dr, Ste F-4, Indianapolis, IN 46227, 317 783-7474.

INDIANA, North of Indianapolis: Immediate full-time position and directorship opportunity available in newly-renovated emergency department. Hourly salary, flexible scheduling, malpractice insurance provided. Locum tenens opportunities also available. For more information, contact Emergency Consultants, Inc, 2240 S Airport Rd, Ste 101, Traverse City, MI 49684, 800 253-1795, in Michigan 800 632-3496.

IOWA: Immediate full-time position available for emergency physician to staff two hospitals, a Level II trauma center and a regional resource hospital, in Sioux City. ACLS ATLS required. Excellent staff backup with attractive hourly wage. Send CV to Don E Boyle, MD, 2918 Hamilton Blvd, Sioux City, IA 51104.

IOWA: Physicians for neighborhood clinics in Des Moines. Internal medicine, family practice, and emergency physicians preferred. Scheduled hours. Competitive compensation package. PO Box 65574, West Des Moines, IA 50265, or call 515 223-9378.

LOUISIANA, New Orleans: Position for a full-time board certified -prepared emergency physician. Call or write John S Sabella Jr, MD,

2025 Gravier St, New Orleans, LA 70112; 504/524-6489.

MAINE: Director of emergency department needed for modern multi-facility, 233-bed hospital system with multi-specialty medical staff located in a progressive university town in northern Maine. Board-certified/-prepared candidates preferred. Competitive salary offered and excellent fringe benefits available. Please forward CV to Richard Wilson, MD, Medical Director, The Aroostook Medical Center, PO Box 151, Presque Isle, ME 04769.

MAINE: Immediate opening for emergency physician. Prefer emergency medicine boarded or family practice/internal medicine boarded with emergency department experience for moderate-volume emergency department. Teaching opportunities for Maine-Dartmouth FP residents, PAs, and EMTs. Located in Central Maine Lakes Region between the ocean and the mountains. Excellent recreational activities. Contact Marshall T Chamberlin, MD, 3 Colony Rd, Augusta, ME 04330; 207/623-4089 or 207/623-4711 ext 302.

MARYLAND: Career-oriented emergency department professionals seek qualified physicians to staff emergency departments in Coastal Maryland, southern Pennsylvania, and Washington DC area. Attractive compensation package. Respond with CV to Sally Bowen, FEMSA, 6227 Executive Blvd, Rockville, MD 20852; or call 301-984-0353.

MARYLAND, Baltimore: High quality group with two stimulating and contrasting practice locations in community teaching hospitals, seeks career emergency physicians. Modern facilities, excellent backup. Position entails clinical teaching and administrative duties. Excellent salary, benefits, working conditions. Prefer emergency medicine board certified/prepared, residency trained in emergency medicine or FP, IM, or GS with experience. ACLS. ATLS. Reply in confidence to ACEP Box 877, PO Box 619911, Dallas, TX 75261-9911.

MARYLAND, Baltimore: Night person/colleague sought by dynamic group based at two community/teaching hospital locations. If you are that special person that prefers night duty and wants to be a full member of the "team," please contact us. Excellent salary, benefits, and working conditions. Prefer emergency medicine board certified/prepared, residency trained in emergency medicine or FP, IM, or GS with experience. ACLS. ATLS. Reply in confidence to ACEP Box 876, PO Box 619911, Dallas, TX 75261-9911.

MARYLAND, Baltimore: Very successful, well established, independent, fee-for-service group based in busy, modern suburban community hospital, seeks career EM physician. Competitive salary and schedule. Board certified/prepared in EM or related field. Immediate availability. Send CV to Eric Toner, MD, Box 5488, Towson, MD 21204.

MASSACHUSETTS: Expanding independent group staffing emergency department with 40,000 annual patient visits seeks additional associates. Family-oriented community within 30 minutes of Boston, beaches, and within 90 minutes of skiing and Cape Cod. Reply in confidence to Joel B Hellmann, MD, Director, Emergency Department, Bon Secours Hospital, 70 East St, Methuen, MA 01844; 617/687-0151.

MASSACHUSETTS: 40,000+ annual visit emergency department seeking full-time physician. Must have minimum three years ED experience. Prefer board certification. Location: Eastern Massachusetts. Please send CV on first response to ACEP Box 923, PO Box 619911, Dallas, TX 75261-9911.

MASSACHUSETTS: Full-time emergency and ambulatory care physicians in Springfield, Massachusetts, area. Available July 1985. Emergency department residency or experience equivalent preferred. Salary competitive, excellent benefits. Contact James D Anderson, MD, Emergency Physicians, Inc, PO Box 662, E Longmeadow, MA 01208, or call 413/525-1554.

MASSACHUSETTS: Immediate opening. Excellent opportunity for board-certified/-prepared emergency physician. University-affiliated community hospital. 45,000 visits. Desirable location 20 miles from Boston. Highly attractive compensation package and schedule. Send CV in confidence to T Blair, MD, FACEP, Chief of Emergency Services, Brockton Hospital, 680 Centre St, Brockton, MA 02402.

MASSACHUSETTS: Independent group of five emergency medicine residency-trained physicians seeking a sixth member. ED volume of 20,000 serviced by Cape and Islands EMS system. Guaranteed salary and comprehensive benefit package are competitive with area. Coastal location with easy commute to Boston and Providence. Send CV to ACEP Box 820, PO Box 619911, Dallas, TX 75261-9911; or call 617/758-2235.

MASSACHUSETTS, Worcester: Emergency medicine attending wanted at 341-bed major teaching affiliate of U-Mass Medical Center. 30,000+ visits/year, regional resource hospital. BC/BP preferred; academic appointment available for qualified applicants. Responsibilities include teaching and patient care in concert with outstanding medical housestaff. EM residency planned July, 1987. Send CV to Gordon W Josephson, MD, Chief, Emergency Medicine, Worcester Memorial Hospital, 119 Belmont St, Worcester, MA, 01605; 617/793-6291.

MICHIGAN, Emergency Physicians: Full- or part-time positions in rural southwest Michigan. Competitive reimbursement; ACLS required, ATLS preferred. Nice rural community. Please send CV to ACEP Box 928, PO Box 619911, Dallas, TX 75261-9911.

MICHIGAN: Exceptional opportunity for career-minded, board-certified emergency physician. Recent expansion in volume of this emergency department requires qualified addition to our experienced staff. Position offers excellent benefits and remuneration, as well as ready access to Michigan's year-round vacationland. For additional information, please send resume or call, Louis E Zelle, President, St Luke's Hospital, 705 Cooper, Saginaw, MI 48602; 517/771-6000.

MICHIGAN: Full- and part-time positions, including directorships, available in our southeastern Michigan freestanding immediate care centers. Paid malpractice and stock ownership included in an excellent reimbursement package. Write Family First Medical Centers, 325 E Eisenhower Parkway, Ann Arbor, MI 48104; or call Margaret Turner, 313/729-5780.

MICHIGAN: Rapidly expanding group of emergency physicians with opportunities for qualified full-time and part-time physicians. Salary with many fringes including stock in PC. Send resume for complete details. MEDIC PC, PO Box 1116, Grand Rapids, MI 49501.

MICHIGAN: Residency-trained or board-certified emergency physician for full-time position in spring '1986. Teaching hospital. To join well-established group in southwest Michigan. Outstanding residential community and superlative recreational and cultural opportunities. Please send CV to ACEP Box 912, PO Box 619911, Dallas, TX 75261-9911.

MICHIGAN: Urban/suburban community teaching hospital. Career

emergency physician. Prefer ABEM certified/prepared. Department provides medical control for ALS system. Attractive compensation package. Send CV to Joseph L Schirle, MD, Pontiac General Hospital, 461 W Huron, Pontiac, MI 48053; or call 313/857-7440.

MICHIGAN, Ann Arbor/Detroit Area: Looking for career-oriented emergency physicians board certified/prepared in emergency medicine, internal medicine, surgery, or family practice. Directorships with stipends available. Excellent compensation including malpractice insurance. Contact Emergency Consultants, Inc, One Windemere Pl, Petoskey, MI 49770, 800 253-7092, or in Michigan 800/632-9650.

MICHIGAN, Detroit Area: Full-time positions available at 24,000-visit community emergency department. Contracting group operates Class I trauma center in area and university emergency medicine residency program. Fee-for-service compensation with occurrence-based malpractice provided. Contact Brooks F Bock, MD, Medical Center Emergency Services, PC, 4201 St Antoine, Detroit, MI 48201, 313 494-3330.

MICHIGAN, Flint: Residency-trained or board-prepared physician needed to join full fee-for-service group. Compensation over $90K plus benefits. 33,500 annual visits in established residential area adjacent to University of Michigan-Flint campus. Centrally located to Detroit, Ann Arbor, and recreational areas. Send CV to SJHS Emergency Services, 12426 Moceri Dr, Grand Blanc, MI 48439, 313 694-3921.

MICHIGAN, Grand Rapids: Well-established group needs additional member for full-time position. 350-bed hospital with 30,000 visits per year. ED group all board certified in emergency medicine. Excellent remuneration and pension plan in congenial group. Applicant must be residency trained in emergency medicine or board certified in emergency medicine. City has many cultural advantages and west Michigan area is exceptional for its recreational opportunities and outdoor sports. Send CV to William C Daney, MD, Chairman, Dept of Emergency Medicine, St Mary's Hospital, 200 Jefferson, SE, Grand Rapids, MI 49503, phone 616 774-6789 or 616 949-9536.

MICHIGAN, Saginaw: Opportunity for EM residency-trained or highly experienced emergency physician to join progressive, established five-man group covering 255-bed teaching hospital in new ED. Hospital provides tertiary care for trauma, neurosurgery, and burn patients. Academic appointment through Michigan State University available for qualified individuals. ED is medical control for county ALS system. Group has newly established urgent care center and excellent compensation. Contact GM Mailman, MD, Dept of Emergency Medicine, 517 776-8200, or AJ Ziner, 517 776-8300, St Mary's Hospital, 830 S Jefferson, Saginaw, MI 48601.

MISSISSIPPI, Greenville: Delta city of 50,000 surrounded by lakes and recreational areas. Flexible schedules will accommodate vacations and hunting season. Income range of $80-100,000 depending on pathology and volume. Busy ED with high degree of trauma sees 18,500 patients per year and has shown steady growth since 1976. New 11,000 sq ft department in 250-bed medical center which serves as EMS satellite center to University of Mississippi. ED sees 98% of patients with excellent medical staff backup. This is a fee-for-service opportunity where income potential is not limited. Fischer Mangold provides most malpractice coverage, CME, potential group incentive after 3 years, and directorships with incentive base. Contact Ken Baker, Director of Physician Recruitment, Fischer Mangold Group, PO Box 788, Pleasanton, CA 94566; 800 227-2092, in California 415/484-1200.

MISSOURI: Associate needed for very busy family and occupational practice located in northwest Missouri. Guaranteed minimum compensation plus substantial incentives and benefits. Excellent potential for equity position for the right individual. Considerable growth and expansion opportunity. Career-oriented physicians send resumes to Health Innovators, 8550 NW 48th St, Ft Lauderdale, FL 33321, 305 748-9100.

MISSOURI: Well-qualified emergency physician needed for a full-service, acute care facility which has a service area population of 95,000. Emergency department patient volume is approximately 12,000 annually, and the total compensation package is approximately $85,000 annually. For additional information, please send CV to Cecelia Cleary, Emergency Medical Services, 3212 Central Ave, Kansas City, MO 64111, or call 800 821-5147 or 816 561-1025.

MISSOURI, Springfield: Nine-man group desires a tenth person to staff the emergency departments of Cox North (300 bed) and Cox South (500 bed). Above average salary plus 15% profitsharing plan. Life, medical, and disability insurance and a medical reimbursement plan. Five weeks paid vacation, an average 37-hour week. Malpractice paid. Shane L Bennoch, MD, Emergency Dept, Cox Medical Center, 1423 N Jefferson, Springfield, MO 65802, or call collect 417/836-3193 (office) or 417 753-2683 (home).

MISSOURI, St Louis: Full-time staff and directorships exist at five new St Louis metropolitan area health-care facilities. Openings include hospital-based emergency medicine positions, HMOs, or freestanding urgent care centers. Benefits include flexible scheduling, competitive income, professional liability insurance, moving allowance,

CME tuition, ACLS, ATLS, and ACEP membership dues reimbursement. For details contact Debbie Kotaki, Spectrum Emergency Care, Inc, PO Box 27352, St Louis, MO 63141; 314/878-2280 or 800/325-3982 (toll free)

MISSOURI, St Louis Metro Area: Need BC IM, FP, or EM physician for moderate volume Illinois ED. ACLS required, ATLS strongly recommended. Expanding organization with ED and industrial medicine exposure. Opening in September. For further information, send CV in confidence to ACEP Box 934, PO Box 619911, Dallas, TX 75261-9911.

MONTANA: Expanding physician-owned emergency group has opening for full-time career-oriented emergency physicians in western Montana. Flexible work schedules, excellent working and living conditions. Contact Donald Cantway, MD, or Sheldon K Truax, 307/745-3169, or send CV to IntraWest Medical Services, PO Box 1649, Laramie, WY 82070.

NEVADA, Lake Tahoe Area: Board-certified/-prepared emergency physician needed for moderate volume emergency department. Facility is base station. Excellent staff backup. Fee for service. Paid malpractice. Please send CV to Dr Richard Harvey, Carson-Tahoe Hospital Emergency Dept, 1201 N Mountain St, Carson City, NV 89701.

NEW HAMPSHIRE, Concord: Emergency physician to help man hospital-based urgent care center and rotate through busy emergency department. 300-bed Level II trauma center. Competitive salary. Send CV to Concord Emergency Medical Associates, Concord Hospital, 250 Pleasant St, Concord, NH 03301.

NEW HAMPSHIRE, Manchester: Full-time position available July 1984 for experienced ED physician. Prefer board certified or prepared. One hour from Boston or the White Mountains. Modern Level II trauma center. 27,000 annual visits, excellent compensation. Send CV and contact Jim Young, MD, Elliot Hospital, 955 Auburn St, Manchester, NH 03103, 603 669-5300.

NEW JERSEY: Career-oriented emergency medicine practitioners wanted for full-time positions in emergency departments in northern and central New Jersey. Certification or qualification in emergency medicine or related specialty required, full-time emergency experience preferred. Send CV to Emergency Medical Associates of New Jersey, PA, 651 W Mount Pleasant Ave, Livingston, NJ 07039, Attn: Louise Pirone.

NEW JERSEY, Emergency Physician: Immediate opening for full-time emergency physician. Board certification or residency training in emergency medicine preferred. Partnership available in independent fee-for-service group in one of New Jersey's most prestigious hospitals located in northern New Jersey. Excellent compensation. Reply in confidence to ACEP Box 933, PO Box 619911, Dallas, TX 75261-9911.

NEW JERSEY: Full-time and part-time emergency department positions in new ED of 410-bed JCAH accredited hospital. Board certified/prepared in emergency medicine, family practice, internal medicine, or surgery with minimum of two years emergency department experience. Liberal salary and benefits package. Send CV to Joseph J Levinsky, MD, Director, Emergency Services, Memorial Hospital of Burlington County, 175 Madison Ave, Mt Holly, NJ 08060. Equal Opportunity Employer M/F.

NEW JERSEY: Full-time position. 370-bed acute care hospital in northern New Jersey/metropolitan New York area, located five miles from Manhattan. ED volume approximately 21,000. Paramedic base station with backup in all specialties. FFS group. $90,000 first year for 36-hour week plus 10 hours/month administrative duties. Partnership/FFS second year. Expansion into satellite facility expected this year. ABEM-certified or emergency medicine residency-trained physicians only. Prefer current NJ license. Reply in confidence to ACEP Box 910, PO Box 619911, Dallas, TX 75261-9911.

NEW JERSEY, Central: Full-time position for a physician BC/BP in emergency medicine or a related specialty with ED experience. 37,000+ visits/year in a 420-bed major teaching affiliate of UMDNJ/Rutgers Medical School. Double coverage for twelve hours/day. Resident and medical student teaching plus involvement in regional EMS necessary. Starting salary approximately $92,000/year. Send CV to ACEP Box 931, PO Box 619911, Dallas, TX 75261-9911.

NEW JERSEY, SOUTHEASTERN PENNSYLVANIA: Expanding group needs full-time career physicians. ATLS, ACLS and experience required. Competitive salary plus excellent benefit package. Send CV to ECEP, 75 Atsion Ct, Medford, NJ 08055.

NEW MEXICO, Northwest: Immediate opening for qualified physician in Level II trauma center in the beautiful Four Corners area of New Mexico. Recreational opportunities abound. Excellent compensation package. Board certified -prepared applicants send CV to JE Nordstrom, PO Box 1397, Farmington, NM 87499 or call 505 325-1836.

NEW MEXICO, Silver City: September opening for board-qualified or experienced emergency physician to join regional medical center ED group. Immediate partial partnership, excellent growth potential, beautiful environment, serves 100-mile radius, prehospital teaching opportunity. William Neeny MD, Box 3050, Silver City, NM 88062, 505 536-9949.

NEW YORK: Immediate opening for full-time, board-certified -prepared emergency physician. Prefer ED-residency trained, ACLS, ATLS certified. Progressive, well-equipped, 300-bed community hospital in beautiful northern Westchester County with 23,000 ED visits/year. 35 miles from NYC, 20 miles from LI Sound. Excellent salary and fringe benefits. Send CV to Robert Marcus, MD, Chief, Emergency Department, Northern Westchester Hospital Center, Mt Kisco, NY 10549, 914 666-1776.

NEW YORK, New Paltz: Seeking full-time experienced or residency-trained physicians, ATLS and ACLS certified for state-of-the-art FEC in

beautiful Mid-Hudson Valley, 80 miles from New York City. Start date is July 15, 1985. Package includes health, life, disability, and malpractice insurance. $30/hour. Attractive scheduling and potential profitsharing. Send CV/inquiries to Gary W Greer, MD, RD 3, Box 44A, Cogan Station, PA 17728; 717/494-0420.

NEW YORK, Rochester: 400-bed university-affiliated community teaching hospital seeking experienced or residency-trained emergency physician. Department sees 40,000 patients per year. New physical plant in planning stages. Salary and starting date negotiable. Send CV in confidence to Richard S Krause, MD, Director, Emergency Division, Department of Ambulatory Services, The Genesee Hospital, 224 Alexander St, Rochester, NY 14607.

NEW YORK, NEW JERSEY, PENNSYLVANIA: Excellent opportunity for career-oriented physician preferably with training in surgery and/or emergency medicine and two years experience to work in pleasant atmosphere of freestanding emergency treatment offices. Competitive salary and benefit package. Medical director positions available. Contact Richard L Levine, MD, President, PriMed, Inc, 2500 Brunswick Pike, Lawrenceville, NJ 08648; 609/771-6663.

NORTH CAROLINA: Community-oriented emergency medicine group seeking career full-time emergency physicians for coverage of two local hospitals (each with 16,000 ED visits/year) in NC foothills. Excellent salary and benefits. Must have excellent PR abilities and be willing to live in area and support hospital and community interests. Respond to Mountain Emergency Physicians, PA, 215 Willowbrook Rd, Lenoir, NC 28645; 704/758-9583.

NORTH CAROLINA: Emergency department positions available throughout the scenic Blue Ridge Mountains of western North Carolina. A paradise for those who enjoy skiing, hiking, canoeing, and fishing. Easy access to major cities. Low and moderate volume facilities with good medical staff support. Excellent compensation and professional liability insurance provided. Independent contractor status. For further information contact Doug Riley, Coastal Emergency Services, Inc, Ste 217, Executive Park, Asheville, NC 28801; or call collect 704/253-1256.

NORTH CAROLINA: Emergency physician sought for 500+ bed teaching hospital. Will work with five other physicians to handle a patient load of approximately 35,000 patients annually, primarily trauma. Board certified/prepared in emergency medicine. Centrally located between the mountains and coast, with access to the Research Triangle facilities and three major universities. Abundant cultural and social opportunities. Competitive compensation package. Send CV to Nancy Nelson, Personnel Recruiter, Wake County Hospital System, Inc, 3000 New Bern Ave, Raleigh, NC 27610; or call 919/755-8140. An Equal Opportunity Employer.

NORTH CAROLINA: Full-time, career-oriented emergency physicians are now being sought for positions in medium-sized, full-service hospital (300-550 beds) with active emergency departments, (25,000-35,000 visits per year), as well as in freestanding (private) EmergiCenters. Involvement in management, pre-hospital (EMS) system and resident teaching is available and encouraged. Excellent salary and complete benefits are provided to the members of this stable group of emergency physicians. For more detailed information please respond with complete CV to SEMA, PA, PO Box 12322, Ste 3, 10 Park Plaza, Research Triangle Park, NC 27709.

NORTH CAROLINA: Full-time emergency physician needed at 100-bed hospital located one hour from Raleigh/Durham area and near large recreational lake in small pleasant community. 12,000 annual ED visits. Excellent medical backup. Competitive compensation with malpractice provided. Independent contractor status. For further information contact Coastal Emergency Services, Inc, PO Box 2508, Durham, NC 27705; 919/383-0367; 800/672-1665 in NC; 800/334-3306 in US.

NORTH CAROLINA: Full-time emergency physicians needed for 160-bed hospital with good medical staff support. Located close to Charlotte and 1 2 hour from the world-famous Pinehurst and Southern Pines golf courses. 16,000 ED visits annually 24-hour shifts. Competitive compensation with malpractice provided. Contact Coastal Emergency Services, Inc, PO Box 2508, Durham, NC 27705; 919/383-0367; 800/672-1665 in NC; 800/334-3306 in US.

NORTH CAROLINA: Medical director needed for 135-bed hospital with excellent medical staff support. Located 45 minutes from Charlotte where excellent shopping, educational and cultural opportunities abound. 13,000 ED visits annually 24-hour shifts. As director, benefit package and malpractice insurance are provided. Contact Coastal Emergency Services, Inc, PO Box 2508, Durham, NC 27705; 919/383-0367; 800/672-1665 in NC; 800/334-3306 in US.

NORTH CAROLINA: Modern 166-bed hospital, less than one hour from the North and South Carolina beaches and major university, needs full-time emergency physician. Good medical staff support. 26,000 annual ED visits. 12-hour shifts with physician assistant support. Independent contractor status. Competitive compensation with malpractice insurance provided. Contact Coastal Emergency Services, Inc, PO Box 2508, Durham, NC 27705; 919/383-0367. 800/672-1665 in NC; 800/334-3306 in US.

NORTH CAROLINA: Physician to join established group in historic piedmont town short distance from any of three major cities. Busy ED with new modern facility. US educated with residency or experience in emergency medicine or family practice preferred. Competitive compensation including malpractice. Flexible schedule. Send CV or contact David Skowronek, MD, 11 Spicewood Ln, Salisbury, NC 28144; 704/636-7044.

NORTH CAROLINA, Fayetteville: Seek physician/director and staff physician to complete new full-time emergency department group at new, private, community hospital with good working conditions and full specialty backup; prefer ABEM certified/prepared with ABFP, ABIM, or ED residency plus full-time experience; competitive salary and benefits; ground floor opportunity in growing ED. Please contact Douglas I Hammer, MD, PO Box 30788, Raleigh, NC 27622; 919/848-4757.

NORTH CAROLINA, High Point: Seek career-oriented emergency physician to join full-time emergency department group at 300+ bed community hospital with good working conditions and full specialty backup; prefer ED residency, family practice, internal medicine board certification plus full-time ED experience; competitive salary, bonus plan and benefits; outstanding opportunity for well-qualified individual. Contact Jeff Tope, MD, PO Box 5309, High Point, NC 27262; 919/292-4430.

NORTH CAROLINA, Lexington: Residency-trained physician in internal medicine, emergency medicine, or family practice for modern hospital with 21,000 emergency department visits per year. Also, urgent care work available. Competitive salary and benefits. Locum tenens or full-time available. Send CV to FESPA, PO Box 5856, Winston-Salem, NC 27103.

Oklahoma Can Give You Something To Write Home About

Like more than a million acres of water, and more shoreline than the Atlantic and Gulf shorelines combined. Water for swimming, boating, skiing; fishing, canoeing or sailing.

A healthy lifestyle; plenty of room to grow. Excellent schools whose students consistently score above the national average. Abundant natural resources. Central location. Temperate climate. An industrious labor market that is among the most productive and highly skilled in the nation.

Need full-time physician for our second FEC. Board-certified or prepared in EM or FP.

Join a well-established, stable group practicing quality emergency medicine in Oklahoma's beautiful Green Country. Affiliated with the largest hospital, busiest ED in the state; top quality support staff.

Tremendous growth potential. Administrative and teaching medical students/residents if desired.

To begin summer 1985. Excellent salary and benefit package.

Contact Dr. Howard Roemer, Medical Director, Emergency Care, Inc., 2929 S. Garnett, Tulsa, OK 74129. (918) 665-1520.

You'll find Oklahoma really is something to write home about.

NORTH CAROLINA, Raleigh: Seek career-oriented emergency physician to join full-time emergency department group at excellent private, community hospital with good working conditions and full specialty back-up, university affiliations encouraged; prefer family practice, internal medicine board certification or ED residency plus full-time ED experience, competitive salary, pension/profit sharing plan, and excellent benefits, outstanding opportunity for well-qualified individual. Please contact Douglas I Hammer, MD, PO Box 30788, Raleigh, NC 27622, 919 848-4757

OHIO, Assistant Director: Local (one hospital) emergency medicine group, managing 16,000 annual visit ED in a 240-bed community hospital, is seeking full-time assistant director. Hospital is located in community of 40,000 residents and is one of the wealthiest per capita areas in the state. Assistant director will assume several administrative duties in department and assume acting directorship when current director is out of town. First year compensation of $84,000 plus an excellent benefit package for average 42-hour week. Junior partnership will be available after six months and senior partnership after two years. Please send CV to Daniel Stern and Associates, The Medical Center East, Ste 240, 211 N Whitfield St, Pittsburgh, PA 15206, or inquire directly by calling 800 438-2476, or in Pennsylvania 412 363 9700

OHIO: New hospital in "our town" USA. Tree-lined streets, restored mansions, summer theater, with several colleges and universities in the area. Approximately one hour from Columbus and city life. ED sees between 900-1,000 patients per month with good medical staff backup. Excellent potential for volume growth as function of committed, involved, and local residing ED physician. Average hourly earnings $40.00 or approximately $80,000 per year. Physician remuneration is fee-for service and is not limited in potential. We are a nationwide group offering CME, group incentive after 3 years, individualized scheduling, directorships, and contract management. Contact Ken Baker, Director of Physician Recruitment, Fischer Mangold Group, PO Box 788, Pleasanton, CA 94566, 800 227 2092, or in CA 415 484 1200

OHIO: Pediatric emergency physician sought by emergency physician corporation. Immediate position available in an academic institution. Please send CV to PO Box 30569, Cleveland, OH 44130

OHIO, Cincinnati: Well-established, fee-for-service EM group seeking ABEM-certified career-minded physician for [illegible]. Compensation package approximately 100K. Paid vacation and conference time. Good medical backup. Double coverage every day. Malpractice insurance and pension plan provided. Opportunity for full partnership after 1 year. Please send CV to Allan Packer, MD, 1507 Hollywood Ave, Cincinnati, OH 45224

OHIO, Cleveland: Our caseload is up. Medical Emergency Services operates freestanding urgent care centers and also staffs hospital emergency departments. Our first urgent care center is one of the most heavily used facilities in all of Ohio. We will be opening two additional centers within the next 12 months. We offer the opportunity of practicing emergency medicine in a pleasant and supportive atmosphere with an attractive case mix and top notch staff. You work hard, but have regular hours and an excellent salary. After we both have had some experience together, there is opportunity for stock participation in our organization. If you want to concentrate on practicing medicine and earn a good income without the hassle and expense of running an office, then this can be the opportunity for you. Please send CV to Medical Emergency Services, Inc, 6133 Rockside Rd, Ste 10, Independence, OH 44131, or call 216 642-1400

OHIO, Cleveland and Suburbs: Emergency group practice seeks full-time and part-time physicians for urgent care centers. Send resume to PO Box 30569, Cleveland, OH 44130

OHIO, Marion: Established, well-developed multi-hospital group is seeking an additional experienced emergency physician for a position in a 122-bed tertiary care hospital emergency department. Annual patient volume 10,000-12,000. New modern ED facility completed in 1981. Excellent guaranteed income with incentive compensation program plus paid professional liability insurance. Contact EMS, 4010 Dupont Circle, Ste 700, Louisville, KY 40207, or call toll-free 800 626-2040

OHIO, Massillon: Full-time position available in a progressive 290-bed hospital with a modern and new emergency facility. Minimum two years EM experience required, along with a current Ohio license, ACLS and ATLS certificates. Excellent salary and benefits. Send curriculum vitae to Director of Emergency Department, Massillon Community Hospital, Massillon, OH 44646, or call 216 832 8761, ext 5227. EOE m/f

OHIO, Metropolitan Cleveland and Northeast: Directorship and staff physicians. Seek board-certified/-prepared emergency physicians for staffing of urban and suburban hospitals. Emergency residency training or at least three years experience in emergency medicine highly recommended. Keen interest in continuing education desired. Corporation offers superior compensation and benefits package. Paid benefits include malpractice, health, life, dental and disability insurances, pension and profit sharing plans, and educational reimbursement. Advancement to shareholder status with enhanced benefits and corporate decision making for those who excel. The corporation is democratically structured with opportunity for advancement to shareholder status. Outstanding position for well qualified individual. Please send CV to PO Box 30569, Cleveland, OH 44130, 216 842 7990

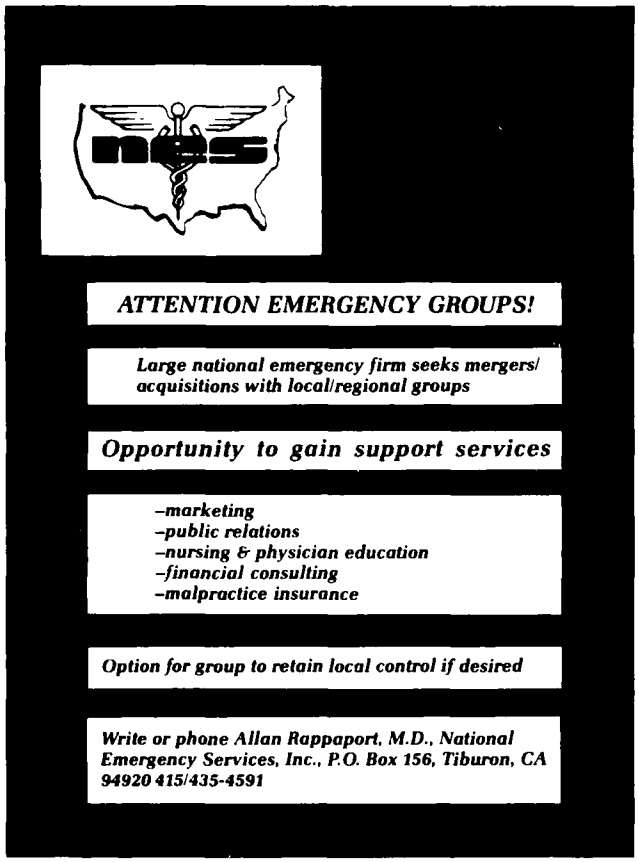
OHIO, Northeast: Academic institution seeking board-prepared and residency-trained staff physicians for a planned emergency medicine residency program. 41,500 volume. Corporate fee-for-service compensation package worth over $100,000. Please send CV to PO Box 30516, Cleveland, OH 44130, or inquire at 216 747 0777, ext 4466

OHIO, Northeast: BC/BP and/or residency trained emergency physician to join group staffing a full-service teaching hospital ED, 35,000 visits/year, superior compensation commensurate with qualifications. Send CV to ACEP Box 927, PO Box 619911, Dallas, TX 75261-9911

OHIO, Northeast: Directorship and staff positions in emergency department. Must be residency trained (board prepared) or board certified in emergency medicine. Send CV to PO Box [illegible], Cleveland, OH 44101-[illegible]

OHIO, Southwestern: [illegible] established [illegible] staff [illegible] emergency departments each with 20,000 [illegible] visits. [illegible] Minimum two [illegible] years emergency department experience required [illegible] ABEM preferred [illegible] MD [illegible] Emergency [illegible]

OKLAHOMA, Tulsa: [illegible]



Tulsa has access to all types of outdoor recreation. Send resume to Eastern Oklahoma Emergency Physicians, Inc, 1923 S Utica, Tulsa, OK 74104, or call collect 918/744-2969.

OPPORTUNITIES: Nationwide for directors and staff emergency physicians in private group, academic or hospital based practices. Excellent guaranteed salaries and benefit packages. Forward CV with objectives and geographic preference to Physician Registry, Emergency Medicine, PO Box 1336, Findlay, OH 45840.

OREGON: Full-time emergency physicians needed for northeastern Oregon location. Well-equipped, well-staffed emergency department; patient volume 10,000/year. Hourly compensation; malpractice provided. *Superb recreational opportunities.* Send CV to L Poschman, Physician Services, Northwest Emergency Physicians, 11808 Northup Way, Bellevue, WA 98005; 206/828-6799.

PENNSYLVANIA: Emergency physician system. Needs several full-time emergency physicians for western Pennsylvania area emergency departments. Independent contractor arrangements. The system is on a fee-for-service basis. Contact 412/228-3400 for interview appointment.

PENNSYLVANIA: Immediate full-time opportunity for a physician in a 175-bed community hospital emergency department with approximately 25,000 annual visits. Located 20 miles northwest of Pittsburgh and ten minutes from the Greater Pittsburgh Airport, Aliquippa Hospital is a progressive community hospital. Emergency department experience required. Board certification preferred for this position. Competitive salary, excellent benefits, and paid malpractice insurance. Send CV to William Donatelli, Aliquippa Hospital, 2500 Hospital Dr, Aliquippa, PA 15001.

PENNSYLVANIA: Progressive 450-bed teaching hospital seeks emergency physician with three years administrative experience to chair newly renovated department of emergency medicine. Volume 30,000 visits. Excellent compensation and benefits. Lovely community for family life. Applicant should be board certified/qualified in emergency medicine. Contact Jerry Silver, Vice President/Patient Services, Conemaugh Valley Memorial Hospital, Johnstown, PA 15905-4398, 814/533-9717.

PENNSYLVANIA, Chester: Full-time position (40 hours per week) available now with fee-for-service emergency medicine group at 454-bed teaching hospital with approximately 40,000 emergency department visits annually. Prefer board-certified -prepared physician in emergency medicine, internal medicine with ACLS ATLS certification. Competitive salary, paid vacation and conference time, profitsharing and other fringe benefits. Send CV to Emergency Medical Associates, Ltd, 15th & Upland Ave, Chester, PA 19013, or call 215/874-8177.

PENNSYLVANIA, Northeastern: Opportunity for a career-oriented emergency physician in a busy ED with medical command to ALS unit. Located on the Pocono northeast of Pennsylvania. Malpractice paid, subcontractor status. Candidate must be board certified/prepared EM or FP and ACLS certified. Mail CV to AES, Inc, PO Box 2510, Wilkes-Barre, PA 18703, or call 717/825-5333.

PENNSYLVANIA, Northwest: Immediate full-time and potential directorship opportunity available in attractive location. Hourly salary, flexible scheduling, malpractice insurance provided. Locum tenens opportunities also available. For more information contact Emergency Consultants, Inc, One Windemere Pl, Petoskey, MI 49770, 800/253-7092; in Michigan call 800/632-9650.

PENNSYLVANIA, Philadelphia: Due to recent growth in suburban Philadelphia, a director and staff physicians are needed for two moderate- to high-volume hospital-based emergency departments. In addition to a competitive income and flexible scheduling, we are offering paid occurrence malpractice coverage, relocation allowance, CME tuition, licensing fees, and ACEP dues reimbursement. Board qualification or certification preferred. For details contact John Dammrich, Spectrum Emergency Care, Inc, PO Box 27352, St Louis MO 63141; 800/325-3982; 314/878-2280.

PENNSYLVANIA, Philadelphia: Full-time position in major university-affiliated hospital. ED seeing 27,000 patients/year. Staff physicians have faculty appointments with responsibility for patient care and supervision of housestaff and students. Seeking board-certified/-prepared candidates in emergency medicine or primary care specialties with ED experience. Contact Laurence Gavin, MD, Director, Emergen-

ALBERT EINSTEIN MEDICAL CENTER
Northern Division

CHAIRPERSON

DEPARTMENT OF EMERGENCY MEDICINE

The Albert Einstein Medical Center, Northern Division, a 600-bed multidisciplinary acute and tertiary care facility, which is the largest teaching affiliate of the Temple University School of Medicine, seeks to recruit a Chairperson for the newly created Department of Emergency Medicine.

The department sees over 40,000 patients each year and has a major commitment to clinical care, teaching and research. Kindly submit your curriculum vitae to:

PETER MAMUNES, M.D.
Chairman, Department of Pediatrics
Chairman, Emergency Medicine Search Committee

ALBERT EINSTEIN MEDICAL CENTER
NORTHERN DIVISION

York & Tabor Roads
Philadelphia, PA 19141

Equal Opportunity Employer

cy Dept, Presbyterian-University of Pennsylvania Medical Center, 39th and Market Streets, Philadelphia, PA 19104, or call 215/662-9350

PENNSYLVANIA, Philadelphia: Major university affiliated teaching hospital seeks an academically-oriented emergency physician. This 619-bed hospital with a new state-of-the-art emergency department sees 40,000 patients annually. Candidates for this position should be skilled clinicians who are dedicated to teaching medical students and housestaff, and who wish to contribute to the scholarly development of emergency medicine. Board certification/board preparation in emergency medicine is required. Academic appointments are available at Temple University Medical School. Salary and benefits are competitive. Please submit curriculum vitae to Sherman Podolsky, MD, Director of Emergency Medicine, Albert Einstein Medical Center, Northern Division, York and Tabor Rds, Philadelphia, PA 19141.

PENNSYLVANIA, Pottsville: Two hours from major metropolitan areas, 1-1/2 hours from Pocono Mountains. Two full-time emergency physicians needed to complement existing emergency medicine group. Candidates should be board certified/prepared in emergency medicine or internal medicine and possess excellent interpersonal skills. Generous compensation and fringe benefits. Submit resume to Dr Ralph Shaw, Pottsville Hospital and Warne Clinic, 420 S Jackson St, Pottsville, PA 17901.

PENNSYLVANIA, Western: Small community hospital within commuting distance of Pittsburgh seeks full-time career-oriented emergency physician to join two full-time physicians, one ABEM certified, one ABEM prepared; ABEM preparation or certification desirable; 13,000 census, progressive department, flexible scheduling, five full days off per week; competitive compensation package; opening August 1985. Send CV to David J Simon, MD, Director, Emergency Department, Ellwood City Hospital, Ellwood City, PA 16117; or call 412/752-0081.

PENNSYLVANIA, South Central: Emergency physician needed. Command hospital for two-county ALS system. 43,000 ED visits yearly. 570-bed teaching hospital designated as trauma and cardiac center. Paramedic education program. Salary commensurate with qualifications and experience. Heart of the Pennsylvania Dutch country, 50 minutes from Baltimore. Reply to LJ Guzzardi, MD, FACEP, Director of Emergency Medicine, York Hospital, 1001 S George St, York, PA 17405; 717/771-2450.

RHODE ISLAND: Immediate and projected full-time emergency physician sought for university-affiliated hospital with 30,000 annual visits. Responsibilities include supervising and teaching family practice, internal medicine, and surgical residents. Seeking ABEM-certified or qualified. Competitive salary with many extras. Apply to Tony Krembs, MD, Chief of Emergency Medicine, The Memorial Hospital, Prospect Street, Pawtucket, RI 02860. An Equal Opportunity Employer.

SOUTH CAROLINA: Associate needed for very busy internal medicine, family, and occupational practice located in central South Carolina. Guaranteed minimum compensation plus substantial incentives and benefits. Excellent potential for equity position for the right individual. Considerable growth and expansion opportunity. Career-oriented physicians send resumes to Health Innovators, 8550 NW 48th St, Ft Lauderdale, FL 33321.

SOUTH CAROLINA: Full-time position available in August for career-oriented emergency physician. Hospital is modern 285-bed Level II facility near Columbia with 30,000 visits annually. Excellent backup and affiliation with major teaching hospital. Send CV to John Sorrell, MD, Richland Memorial Hospital, 3301 Harden St, Columbia, SC 29203, or call 803/765-7533.

SUNBELT, Greenville, Mississippi: Delta city of 50,000 surrounded by lakes and recreational areas. Flexible schedules to accommodate vacations and hunting season. Income range of $80,000-$100,000 depending on pathology and volume. Busy ED with high degree of trauma sees 18,500 patients per year and has shown steady growth since 1976. New 11,000 sq ft department in 250 bed medical center which serves as EMS satellite center to University of Mississippi. ED sees 98% of patients with excellent medical staff back-up. Excellent for service opportunity where income potential is not limited. Physician Mangold provides most malpractice coverage. CME, [illegible] incentive after 3 years, and directorships [illegible]. Contact Ken Baker, Director of Physician Recruitment, [illegible], PO Box 788, Pleasanton, CA 94566, 800/227-[illegible], in California 415/484-1200.

TENNESSEE, Emergency Physician: Need [illegible] long-established and stable group in Knoxville. Teaching [illegible] specialty backup, excellent compensation package including multiple insurance benefits, profit sharing and pension plans and CME allowance. Work schedule allows ample time off. Send CV to Knoxville Emergency Physicians Group, Blount Professional Building, Ste #6, Knoxville, TN 37920, or call 615/523-6579.

TENNESSEE: Experienced career emergency physician needed to join well-established group in Chattanooga. Excellent salary and fringe benefits. Contact Shawn Gazaleh, MD, Director, Emergency Medicine, 975 East Third St, Chattanooga, TN 37403, 615/778-7628.

TENNESSEE, Chattanooga: Full-time with established multi-hospital group. Excellent salary plus fringe benefit program including medical, disability, life, and malpractice insurance, profitsharing plan, etc. CV to Emergency Medical Associates, PO Box 2538, Chattanooga, TN 37407, 615/629-9795, or Chic Thomas 615/842-0657.

TENNESSEE, Nashville: Emergency department full-time position available at 600+ bed hospital. Must be board certified/prepared in EM or have prior ED experience. Offers physician participation in hospital public relations programs and emergency air transport system. Please submit resume to Emergency Consultants, Inc, One Windemere Pl, Ste 101, Petoskey, MI 49770, 800/253-7092, in Michigan 800/632-9650.

TENNESSEE, Nashville: [illegible] full-time emergency physician needed for [illegible] board certified/prepared in emergency [illegible] ... 90K to start, plus comp time for 15 shifts [illegible] ... Medical Director, MEC Director of Emergency Services. [illegible], TN 37064, 615/791-2176.

TENNESSEE, Nashville: [illegible] needs [illegible] ... $80,000-$90,000 ... [illegible] ... Medical Associates, [illegible].

TEXARKANA — TEXAS AND ARKANSAS: [illegible]

gency positions immediately available for community hospital. Low volume, $30.00/hour, 40-hour shifts available, commuters welcome, malpractice, flexible scheduling. Call Jim Marlin, Southwest Critical Care Associates, 318/688-2902; PO Box 17977, Shreveport, LA 71138-0977.

TEXAS: Full-time emergency position available in modern emergency facility in north central Texas. Fee-for-service with minimum guarantee. Malpractice paid. Two years emergency department experience or equivalent. Send CV and write for application to Emergency Medicine Consultants, 1525 Merrimac Circle, Ste 107, Fort Worth, TX 76107 or call 817/336-8600; metro 429-8881.

TEXAS: Group ED practice opportunity. Completing local group for 185-bed community hospital with 21,000 visits (18,000 last year). Trauma center designation in progress; full specialty backup. On-site FP residency with ED rotation; active nursing education department; and hospital-based paramedic ambulance service require commitment to teaching. US-trained physicians who are nearing or have completed ABEM preparation/certification with high volume ED/trauma experience. One year provisionary status at 95-100K followed by full associate position if compatible. Send CV to ACEP Box 881, PO Box 619911, Dallas, TX 75261-9911.

TEXAS: Physician wanted. Guarantee $30/hour or percentage of gross, whichever is greater. Liability malpractice insurance paid; flexible schedule. Growing community one hour drive from Houston on edge of "Big Thicket." Write LV LeBoeuf, MD, PO Box 7530, Beaumont, TX 77706; call 409/898-2445 or 409/755-2623.

TEXAS, Dallas Area: Associate medical directors needed for FEC expansion in Dallas area by national corporation. Full- and part-time positions also available in existing FECs. Incentive pay plan, malpractice paid. DD Stringer, MD, 14902 Preston Rd, Dallas, TX 75240. 214/980-1010.

TEXAS, Denton, Gainesville, Sherman, and more: Full-time positions available in these growing Texas cities. Small group serves both EDs and FECs. US education required. Call Mrs Neu, Numed Systems, Inc. 817/566-1936.

TEXAS, Fort Worth, Sherman, Cleburne, Azle: Excellent opportunity for physicians with established emergency department group. Experience required. Malpractice paid. Fee-for-service with minimum guarantee. Flexible scheduling. Accepting applications for full- or part-time. Send CV to Emergency Medicine Consultants, 1525 Merrimac Circle, Ste 107, Fort Worth, TX 76107 or call 817/336-8600; metro 429-8881.

TEXAS, Houston: Full-time career position is available in two hospital EDs in north Houston 1960 area. Census 1,000-1,800; competitive compensation, fee for service. Amiable and easy-going emergency physician needed with experience in major trauma and acute care. The physician must have his own malpractice insurance policy. Send CV to Emergicare Associates, 4305 Westheimer, Houston, TX 77027, 713 960-1210.

TEXAS, Houston: Quality-oriented emergency medicine group of board-certified -prepared physicians seeking applications from career-minded emergency physicians. Group staffing three EDs at the present time. Fee-for-service, independent contractor status with minimum hourly guarantee. Consideration given to applicants with US residency training in emergency medicine or at least two years of ED experience. Send CV to STEP, 6910 Fannin, Ste 307N, Houston, TX 77030. 713 795 0681.

TEXAS, Longview, Tyler, Greenville: Full-time positions available in beautiful East Texas. Compensation of $75 000 to $100 000 per year with fee-for-service and hourly guarantee. Flexible scheduling, full support services. Contact Brenda Lancaster, EmCare, 3600 Gaston, Ste 802, Dallas, Tx 75246. In Texas 214 823-6850, out of state toll free 800 527 2145.

TEXAS, Lufkin: Directorship and one full time staff position available in modern emergency department. Beautiful surroundings, of lakes and woods. Directorship package of $100 000 plus. Please contact Keith D Williams, MD, Emergicare Systems Corporation, 3101 S 27th St, Abilene, Tx 79605, 915 695 5440.

TEXAS, Northeast: Hospital ED with 9 500 visits per year. Excellent and cooperative medical staff with wide representation of specialties. Excellent community for family. Opportunity for sharing directorship at early date; possibility for developing group to serve other area hospitals. $30/hour starting, malpractice insurance paid. Send CV to ACEP Box 919, PO Box 619911, Dallas, TX 75261-9911.

TEXAS, Panhandle: Full-time position for physician EM or FP qualified. Progressive new 126-bed hospital with cooperative medical staff; low volume ED; flexible scheduling; 75,000 + range. Call or send CV to Earl Hoffer, MD, Rt 1, Box 11-A, Pampa, TX 79065, 806 665-6166.

TEXAS, San Angelo: Outstanding opportunity in minor emergency/family practice clinics. Guaranteed $100,000 for 4-day week (13-hr days), 50 weeks year. Profit sharing above guarantee. Contact Bill Bass, MD, Shamrock Clinics, 4208 College Hills, San Angelo, TX 76904, 915 942-8611.

TEXAS, Tyler and Longview: Physicians wanted in beautiful east Texas for medical clinics and hospital emergency departments. Hourly vs percentage type reimbursement, malpractice paid. Send CVs to Jane Taylor, 4500 S Broadway, Tyler, TX 75703, or call 214 581 4300.

VIRGINIA: Career emergency physicians sought for full-time emergency department staff positions in 525 bed hospital in piedmont VA. 40 000 annual visits with daily double coverage during the busiest hours. Compensation in the $80 000 range. Independent contractor status, malpractice provided. Contact Sharon Spencer, Coastal Emergency Services, Inc., 101 Buford Rd, Ste 205, Richmond, VA 23235, or call 800 552 6638 in VA, 800 551 1013 in US, or 804 320 7549.

VIRGINIA: Emergency department positions available throughout the scenic highlands of southwest Virginia. A paradise for those who enjoy skiing, hiking, canoeing, horseback riding, fishing, and nature study. Picture the breathtaking vistas of the Blueridge Mountains. Compensation from $60 000-90 000 with ample time off to enjoy the area. Contact Sharon Spencer, Coastal Emergency Services, Inc., 101 Buford Rd, Ste 205, Richmond, VA 23235, 804 320 7549, 800 552 6638 in VA, 800 551 1013 in US.

NORTHERN VIRGINIA, Metropolitan Washington, DC, and Pennsylvania: Full-time and part-time positions available in active EDs and urgicenters. Salary, competitive benefits, malpractice and liability

paid. Please reply to ACEP Box 925, PO Box 619911, Dallas, TX 75261-9911.

NORTHERN VIRGINIA, Metropolitan Washington, DC, and Pennsylvania: Well established physician-owned group practicing emergency medicine over 23 years staffing high volume emergency departments and urgicenters invites experienced physicians who are making emergency medicine their specialty to join dynamic, expanding organization. Emergency medicine residency prepared or ABEM certified given special consideration. Salary and benefits package approximately $70,000-$90,000 first year with progressive increase to full partnership. Potential to grow within organization and management opportunities a real possibility. Please send CV and references to John P. McDade, MD, Alexandria Physicians Group, Ltd., 8101 Hinson Farm Rd., Ste. 209, Alexandria, VA 22306.

VIRGINIA, Richmond: Seeking residency-trained physicians for full-time emergency department positions. Two facilities with a combined patient volume of 50,000 plus. Hourly compensation plus malpractice insurance provided. For more information contact Emergency Consultants, Inc., One Windemere Pl., Petoskey, MI 49770, 800/253-7092, in Michigan 800/632-9650.

VIRGINIA, Southwest Mountains: Full-time position available in medium sized community hospital with 13,000 annual visits. Prefer career-oriented emergency physician. Benefits include attractive hourly compensation, malpractice insurance, CME compensation. Good medical backup. Abundant time off to enjoy scenic area. Contact Twin County Community Hospital, 200 Hospital Dr., Galax, VA 24333, 703/236-8181, ext. 355.

WASHINGTON: Full-time position. ETF located in eastern Washington. Guarantee vs FFS. Directorship available. Contact L. Poschman, Physician Services, 11808 Northup Way, Ste. 100, Bellevue, WA 98005, 206/828-6799.

WASHINGTON, Kennewick: Excellent opportunity to join our fee-for-service group. 24,000 annual visits, active paramedic visits, prefer career-oriented emergency physician with ATLS, ACLS. Position is available now. Send CV to Raymond E. Kania, DO, Medical Director, Emergency Department, Kennewick General Hospital, 900 S. Auburn, Kennewick, WA 99336.

WASHINGTON, Puget Sound: Local independent fee-for-service group staffing low-volume emergency department seeks additional physician, residency trained or with two years experience. Excellent remuneration for volume of just over 10,000. 150-bed hospital with excellent partnership available after one year if mutually agreeable. Respond with CV to Puget Sound Emergency Medical Consultants, Box 97335, Tacoma, WA 98497; or call 206/582-1900.

WASHINGTON, DC: Emergency physicians needed for hospital located in metropolitan DC area. Board qualified in emergency medicine or board certified in the primary specialties with a minimum of 18 months ED experience required. Hourly compensation as an independent contractor with malpractice provided. For further information contact: Linda Johnston, Coastal Emergency Services, Inc., 1730 N. Lynn St., Ste. 401, Arlington, VA 22209; 703/841-0333.

WASHINGTON, DC: Full-time positions available in community hospital emergency departments in the DC, suburban Maryland, and Hackettstown, NJ, areas, run by growing corporation responsive to your needs. Qualifications: personable physicians, board certified/prepared in emergency medicine, with ACLS certification, ATLS preferred. Excellent remuneration and benefits. Send CV to Gary Langston, MD, 9901 Medical Center Dr., Rockville, MD 20850.

WASHINGTON, DC AREA: Immediate employment opportunities available for emergency physicians, family practitioners, and housestaff to service emergency departments and walk-in medical clinics in the suburban MD/VA area. Send CV to Steven Remsen, MD, 8401 Corporate Dr., Ste. 470, Landover, MD 20785; or call 301/731-6948.

WEST VIRGINIA: Immediate opening at a 265-bed acute care hospital located in southern West Virginia and southeastern Virginia serving a 120,000 service area with 18-20,000 annual ED visits. One hundred physicians on staff with major subspecialty cover, including neurosurgeon. 24-hour radiology, laboratory, and cardiopulmonary services. ATLS and ACLS required. Excellent salary and benefit package available. Send CV to ACEP Box 932, PO Box 619911, Dallas, TX 75261-9911.

WEST VIRGINIA, Charleston: Excellent opportunity in emergency/urgent care. Full-time positions available immediately. Volume approximately 25,000 visits per year. Unique set-up or urgent care and emergency care in same setting, double coverage. Prefer career-minded, experienced physicians with residency training in EM, FP, IM, or surgery. Compensation approximately $90,000 plus for approximately 45-hour week. Contact R. Capito, MD, PO Box 432, Dunbar, WV 25064; or call 304/768-3961.

WEST VIRGINIA, Parkersburg: Established five-man emergency department group has immediate opening for physician career oriented in emergency medicine. Physician group provides emergency services to St. Joseph's Hospital Center. Area is located in scenic city of

65,000 with 35,000 annual emergency department visits. Hospital has seven fully-equipped modular advanced life support vehicles and 17 fully-trained paramedics. CV to Van Elliott, MD, Director of Emergency Medicine Services, St Joseph's Hospital Center, 19th St and Murdoch Ave, Parkersburg, WV 26101; 304/424-4111 ext 4222. EOE.

WEST VIRGINIA, Wheeling Hospital: Emergency/Trauma Department. Seventh and last position. 275-bed regional referral hospital with comprehensive 24-hour on call backup. Active trauma program. Double coverage and choice of 8/12-hour shifts. Faculty appointment possible. Six figure package includes benefits, insurance, over six weeks off. Near Pittsburgh. Send CV to Daymon Evans, MD, FACEP, Wheeling Hospital, Emergency/Trauma Center, Medical Park, Wheeling, WV 26003.

WYOMING: Physician-owned emergency group has opening for full-time career-oriented emergency physician. Flexible work schedules, ideal working and living conditions available. Contact Donald L Cantway, MD, or Sheldon K Truax, 307/745-3169; or send CV to IntraWest Medical Services, PC, PO Box 1649, Laramie, WY 82070.

Business Opportunities

EMERGENCY PHYSICIANS: If you are an emergency physician making a steady income, perhaps you might want to consider the possibility of owning medical centers on the side which can realize you a six-figure income per year for approximately 10 hours of work per week. For information call 312/349-4800.

FEE-FOR-SERVICE PATIENT BILLING/MANAGEMENT SERVICES: We specialize in fee-for-service billing and collection for hospital-based physicians and are presently managing accounts nationally with internally-developed programs designed exclusively for this purpose. We have over ten years of experience, and we will put any or all of our services at your group's disposal. For complete information, write Emergency Medical Systems, Inc, 4010 Dupont Cr, Ste 700, Louisville, KY 40207; or call 800/626-2040 or 502/893-8100.

TEMPORARY MEDICAL OFFICE, Minor Emergency Center: 2-wide 60'x14' trailers with walls and counters arranged for a busy family and occupational practice presently seeing 80 patients daily. Owner wishes to sell or lease with purchase option. Currently located in NW Missouri. Contact Health Innovators, 8550 NW 48th St, Ft Lauderdale, FL 33321; 305/748-9100.

1985 PLACEMENT DISPLAY RATES

Size	Dimensions	No. Times	Price
1 page	7" × 10"	1	$1030
1/2 page vertical	3½" × 10"	1	$730
1/2 page horizontal	7" × 5"	1	$730
1/3 page horizontal	7" × 3¼"	1	$560
1/4 page	3½" × 5"	1	$450
1/6 page	3½" × 3¼"	1	$425
1/8 page	3½" × 2¼"	1	$390

An additional charge will be added for typesetting.

Send your placement display advertising to *Annals of Emergency Medicine*, PO Box 619911, Dallas, TX 75261-9911. Deadline for September 1985 display ads is July 19. **Deadline for October 1985 display ads is August 20.**

PLACEMENT ADVERTISING RATES

Sixty words or less, $40 per issue; $2 for each additional word. To determine the cost of your ad, count each group of letters or numbers bounded by spaces as one word. Examples: EM, 1 word; 214/659-0911, 1 word; Ronald L Krome, MD, 4 words. Five dollars per issue additional for American College of Emergency Physicians confidential reply box. Send your placement listing to *Annals of Emergency Medicine*, PO Box 619911, Dallas, TX 75261-9911; 214/659-0911. Deadline for September 1985 placement ads is July 19. **Deadline for October 1985 placement ads is August 20.**

END

DATE

FILMED

FEB.

1988

END

DATE

FILMED

FEB.

1988